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# Pharmaceutical Industry: Hazardous Waste Generation, Treatment, and Disposal

**Environmental Protection Agency, Washington, D C**

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# PHARMACEUTICAL INDUSTRY

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Alkaloids
Medicinal plants
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# PHARMACEUTICAL INDUSTRY

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1976

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# 1.0 EXECUTIVE SUMMARY

## 1.1 INTRODUCTION

This report is the result of a study commissioned by the U.S. Environmental Protection Agency (EPA) to assess "Hazardous Waste Generation, Treatment and Disposal in the Pharmaceutical Industry." This industry study is one of a series sponsored by the Office of Solid Waste Management Programs, Hazardous Waste Management Division. The studies were conducted for information purposes only and not in response to a Congressional regulatory mandate. As such, the studies serve to provide EPA with: (1) an initial data base concerning current and projected types and quantities of industrial wastes and applicable disposal methods and costs; (2) a data base for technical assistance activities; and (3) a background for guidelines development work pursuant to Sec. 209, Solid Waste Disposal Act, as amended.

The definition of "potentially hazardous waste" in this study was developed based upon contractor investigations and professional judgment. This definition does not necessarily reflect EPA thinking since such a definition, especially in a regulatory context, must be broadly applicable to widely differing types of waste streams. Obviously, the presence of a toxic substance should not be the major determinant of hazardousness if there were mechanisms to represent or illustrate actual effects of wastes in specified environments. Thus, the reader is cautioned that the data presented in this report constitute only the contractor's assessment of the hazardous waste management problem in this industry. EPA reserves its judgments pending a specific legislative mandate.

## 1.2 PURPOSE OF THE STUDY

The study had four basic objectives:

1. to determine the nature and quantities of hazardous wastes originating from the pharmaceutical industry (1973) and to project these wastes to 1977 and 1983;
2. to determine the current treatment and disposal practices within the industry;
3. to examine improved control technologies which could be applied to reduce hazards presented by the wastes; and
4. to calculate the cost of implementing three levels of control technology in a typical hypothetical or existing plant. The three levels of technology are:

   Level I – Technology currently applied by typical facilities;

   Level II – Best technology currently employed; and

   Level III – Technology necessary to provide adequate health and environmental protection.

## 1.3 STUDY APPROACH

Our study consisted of four interrelated tasks:

1. Industry characterization (Section 2.0);
2. Waste characterization (Section 3.0);
3. Treatment and Disposal Technology (Section 4.0); and
4. Cost Analysis (Section 5.0).

Since no Federal law (except the Federal Insecticide, Fungicide and Rodenticide Act, Public Law 92-516) has yet been passed requiring industry to obtain and report data on non-radioactive hazardous wastes destined for land disposal, we had to obtain the voluntary cooperation of companies that represented a significant portion of the pharmaceutical industry. Fortunately, the Pharmaceutical Manufacturers Association (PMA) supported the planned attempt to obtain useful information on which EPA's Office of Solid Waste Management Programs could base part of its future planning and programs. The PMA Environmental Control Committee lent us its support and assisted in obtaining the cooperation of several major pharmaceutical producers.

Because the industry had never had to report detailed composition of waste streams, we realized that mailing of questionnaires would not produce usable information. We therefore chose to conduct in-depth interviews and plant inspections at the plants of the cooperating companies. We visited the principal production facilities of companies which represented an estimated 27 percent of the total U.S. sales of ethical pharmaceuticals and an even higher percentage of active ingredient production of the industry. All 14 facilities we visited had multiple plants and multiple operations, so that in all we surveyed more than 35 component plants. Good representative information was obtained on research and development (R&D), fermentation, biological products, organic synthesis, extraction of animal glands, and formulation and packaging operations in the United States, including Puerto Rico. We checked the information we received in the interviews and by letter and confirmed it with the companies. We then extrapolated the collected data to obtain information applicable to the entire industry.

During the course of the study we also visited eight landfills and four contractors that were treating wastes, principally by incineration. We also interviewed 11 contractors by telephone to confirm information obtained from plant visits.

## 1.4 CHARACTERIZATION OF THE PHARMACEUTICAL INDUSTRY

For this report we found it advantageous to characterize the industry by function as well as by SIC codes. The main function of the pharmaceutical industry is to provide delivery of active therapeutic substances in stable, useful dosage forms, such as tablets, injectables, capsules, and the like. However, the overall pharmaceutical industry can be considered to have four functional sections:

1. *Research and Development* (R&D) – The function of R&D is to discover new drugs and to develop and improve formulations of these and older drugs.

2. *Production of Active Ingredients* – This stage involves the production of the basic active drugs in bulk form.

3. *Formulation and Packaging* – Bulk drugs are formulated into dosage forms, such as tablets, ointments, syrups, injectable solutions, and the like, that can be taken or used by patients easily and in accurate amounts.

4. *Marketing and Distribution* – To get pharmaceuticals to doctors, hospitals, pharmacies, and ultimately to the patient or consumer, pharmaceuticals are promoted by pharmaceutical companies and distributed either directly or through wholesalers. Pharmaceuticals promoted by advertising directly to the consumer are called "proprietary pharmaceuticals" and those advertised to the medical, dental and veterinary professions are called 'ethical pharmaceuticals."

The U.S. Department of Commerce has divided the pharmaceutical industry into three SIC codes: 2831, 2833, and 2834. SIC 2834 (Pharmaceutical Preparations) is essentially the same as the Formulation and Packaging function described above. SIC 2833 covers the major portion of bulk active ingredient manufacture. SIC 2831 covers a group of products which were formerly regulated by the Division of Biologics Standards in the National Institute of Health and not by the Food and Drug Administration. Because the manufacturing and isolation procedures are similar to those in SIC 2833 (Medicinals and Botanicals), the SIC 2831 (Biological Products) operations are combined with SIC 2833 for the purposes of this study.

While the Department of Commerce indicated a 1972 total of 1058 plants in the United States manufactured pharmaceutical products, only 416 of those plants had 20 or more employees. These 416 plants were distributed as follows: SIC 2834 – 302 plants, SIC 2831 – 60 plants, and SIC 2833 – 54 plants. Employment in these three SIC categories in 1972* totaled approximately 130,000. Estimated U.S. domestic sales of ethical pharmaceuticals in 1973* were approximately $5.5 billion and sales of proprietary pharmaceuticals were about $1.9 billion.

## 1.5 WASTE CHARACTERIZATION

The largest tonnage of process wastes currently being landfilled comes from the production of antibiotics by fermentation. In the fermentation industry the antibiotics are produced as by-products of the growth of microorganisms (molds and bacteria). During operations to recover the antibiotics, the microorganisms are filtered off, usually with the addition of an inorganic filter aid, such as diatomaceous earth. This discarded product is usually called "mycelium."

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* Employment figures are based on Census of Manufactures data which are published every five years (the last being 1972), whereas sales figures have been estimated by ADL utilizing U.S. Department of Commerce data for 1973 and other sources.

Because mycelium wastes consist only of cells of organisms, filter aid and residual nutrients, the product is not considered hazardous. However, due to the large quantities produced by a typical fermentation plant and the tendency of the mycelium to emit odors on decomposition, the waste can be a nuisance if not properly handled. The fermentation industry likewise produces a high BOD effluent stream, similar to that produced in the brewing industry, that must be treated in an activated sludge system. Neither the mycelium waste nor the biological sludge from treatment of the effluent streams contains significant quantities of hazardous materials.

Hazardous wastes are produced during the recovery of antibiotics in the form of waste solvents and still bottoms. These solvents are usually nonhalogenated and are relatively nontoxic, but they are hazardous due to their flammability.

The production of organic medicinal ingredients represent the major source of hazardous wastes and a significant source of nonhazardous wastes. Of the roughly 90,700 metric tons of organic medicinals (excluding antibiotics) produced in the United States in 1973, only about 34,000 metric tons were produced by the pharmaceutical industry itself. The remainder was produced by closely allied suppliers to the industry. Production of organic medicinals resulted in wastes consisting of filter cakes, carbon, filter paper, sewage process sludge, unrecoverable halogenated and nonhalogenated solvents, and still bottoms.

Wastes produced by the packaging and shipping sections of the industry are mostly glass, paper, wood, rubber, aluminum, and the like, that are discarded. We estimate only a small fraction of 1 percent of this material to be active pharmaceutical ingredient. We further estimate that 75,000 metric tons of this rubbish is disposed of in regular municipal landfills, along with cafeteria wastes, office wastes, and the like.

Goods returned to the pharmaceutical producer are received by the formulation and packaging section of the industry. We estimate that the approximately 10,000 metric tons of returned goods consist of approximately 85% glass, paper, water, and the like. Of the remaining 15% solids, the active ingredient may range from 100% down to approximately 1%. Because of the low concentration of active ingredient in many products and the low toxicity of the active ingredients, the resulting mix of materials disposed of on land is considered nonhazardous. However, a small number of compounds, such as mercurials, controlled drugs, and the like, are segregated and treated by environmentally acceptable methods.

The only hazardous waste of major concern produced in sufficient quantity from R&D installations is waste solvents (1500 metric tons). Because of the generally flammable nature and the wide variety of solvents in the mixed solvents disposed of, all of these materials are considered hazardous. Many of the R&D personnel are scattered in small groups throughout the industry, but some companies may employ from 200 to over 2000 researchers at a single location.

We classified waste streams from the various industry segments as hazardous or nonhazardous according to criteria explained in Section 3.1.2. Estimates of waste quantities are summarized in Table 1.5.

We expect quantities of both nonhazardous and hazardous wastes to increase in proportion to production in the future with no significant effect of air and water guidelines for 1977 and 1983. We estimate production will increase only at a 3% compounded annual rate from 1973 to 1977 due to the present energy shortages and economic recession. We anticipate economic recovery and the passage of national health insurance will take place in 1976. Therefore, we expect production and concomitant wastes to increase at an annual compounded rate of 7% from 1977 to 1983. Waste projections for 1977 and 1983 are also included in Table 1.5.

Approximately 244,000 metric tons of land-destined process wastes (on a dry basis) were produced by the pharmaceutical industry in 1973. The amount of hazardous wastes is about 25 percent of the total waste, or 61,000 metric tons in 1973. The total wastes are expected to grow to nearly 400,000 metric tons per year and hazardous wastes to 100,000 metric tons per year by 1983.

## 1.6 TREATMENT AND DISPOSAL TECHNOLOGY

Approximately 85 percent of total wastes and 60 percent of hazardous wastes are estimated to be treated and disposed of by contractors. Of the total wastes, ADL estimates that 60 percent, or 150,000 metric tons, are finally disposed of on land. About 9 percent, or 5,600 metric tons of the hazardous wastes, are finally disposed of on land. These percentages reflect the extensive use of incineration, both on-site and by contractors off-site, by the pharmaceutical industry. Where possible, materials are recovered for reuse. Also secure chemical landfills and encapsulation are being used now – and will most probably be used in the future – for the disposal of heavy metal wastes and the like, which are too dilute or contaminated for recovery, and general process wastes of a nonhazardous nature.

In the disposal of a major portion of hazardous wastes generated in the pharmaceutical industry, Level I technology will be adequate for Level II and Level III also. This is true for those wastes such as solvents and organic chemical residues that are presently disposed of by incineration. Some other pharmaceutical wastes that are presently landfilled, such as returned goods and rejected product and high inert content wastes, such as filter cakes, may require incineration to meet Level II and III criteria.

The heavy metal wastes or high inert content wastes, such as filter cakes, that contain heavy metals and are presently landfilled, may require further treatment to meet Level II and Level III criteria.

Table 1.6 presents a summary of the treatment and disposal technology levels for pharmaceutical industry process wastes determined to be hazardous.

## 1.7 TREATMENT AND DISPOSAL COSTS

We have calculated costs for "end-of-pipe" treatment and disposal of each hazardous pharmaceutical waste. These costs do not include charges for in-process changes made to

# TABLE 1.5

## ESTIMATES OF PHARMACEUTICAL INDUSTRY GENERATED WASTES FOR 1973, 1977 AND 1983*

(All Figures in Metric Tons Per Year)

| | 1973 | | | | 1977 | | | | 1983 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | |
| **Industry Segment** | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† |
| **R&D** | | | | | | | | | | | | |
| Solvent | – | – | 1,500 | 1,500 | – | – | 1,900 | 1,900 | – | – | 2,700 | 2,700 |
| Total R&D | – | – | 1,500 | 1,500 | – | – | 1,900 | 1,900 | – | – | 2,700 | 2,700 |
| **SIC Code 2833: Production of Active Ingredients** | | | | | | | | | | | | |
| **Organic Medicinal Chemicals (34,000 Metric Tons/Yr)** | | | | | | | | | | | | |
| Biological Sludge (from wastewater treatment) | 47,600 | 476,000 | – | – | 53,600 | 536,000 | – | – | 80,400 | 804,000 | – | – |
| High Inert Content (filter aid, carbon) | 3,400 | 6,800 | – | – | 3,800 | 7,600 | – | – | 5,700 | 11,400 | – | – |
| Contaminated High Inert Content (i.e., filter aid and solvent) | – | – | 1,700 | 3,400 | – | – | 1,900 | 3,800 | – | – | 2,900 | 5,800 |
| Organic Chemical Residues (tars, mud, still bottoms) | – | – | 13,600 | 13,600 | – | – | 15,300 | 15,300 | – | – | 23,000 | 23,000 |
| Halogenated Solvent | – | – | 3,400 | 3,400 | – | – | 3,800 | 3,800 | – | – | 5,700 | 5,700 |
| Non-Halogenated Solvent | – | – | 23,800 | 23,800 | – | – | 26,800 | 26,800 | – | – | 40,000 | 40,000 |
| Heavy Metal Wastes | | | | | | | | | | | | |
| Zinc Compounds | – | – | 2,200 | 2,200 | – | – | 2,500 | 2,500 | – | – | 3,700 | 3,700 |
| Arsenic Compounds | – | – | 450 | 450 | – | – | 500 | 500 | – | – | 750 | 750 |
| Chromium Compounds | – | – | 20 | 20 | – | – | 22 | 22 | – | – | 35 | 35 |
| Copper Compounds | – | – | 4 | 4 | – | – | 4 | 4 | – | – | 6 | 6 |
| Mercury Compounds | – | – | 1 | 1 | – | – | 1 | 1 | – | – | 1 | 1 |
| Total for Organic Medicinal Chemicals | 51,000 | 482,800 | 45,175 | 46,875 | 57,400 | 543,600 | 50,827 | 52,727 | 86,100 | 815,400 | 76,092 | 78,992 |
| Rounded to: | 51,000 | 480,000 | 46,000 | 47,000 | 57,000 | 540,000 | 51,000 | 53,000 | 86,000 | 815,000 | 76,000 | 79,000 |
| **Inorganic Medicinal** | | | | | | | | | | | | |
| Heavy Metals (i.e., selenium waste) | – | – | 200 | 200 | – | – | 225 | 225 | – | – | 350 | 350 |
| **Antibiotics (by Fermentation, 10,000 Metric Tons/Yr)** | | | | | | | | | | | | |
| Mycelium (plus filter aid and sawdust) | 75,000 | 300,000 | – | – | 84,400 | 338,000 | – | – | 127,000 | 508,000 | – | – |
| Biological Sludge | 35,000 | 350,000 | – | – | 39,400 | 394,000 | – | – | 60,000 | 500,000 | – | – |
| Waste Solvent Concentrate | – | – | 12,000 | 12,000 | – | – | 13,500 | 13,500 | – | – | 20,000 | 20,000 |
| Total for Antibiotics | 110,000 | 650,000 | 12,000 | 12,000 | 123,800 | 732,000 | 13,500 | 13,500 | 187,000 | 1,108,000 | 20,000 | 20,000 |
| Rounded to: | 110,000 | 650,000 | 12,000 | 12,000 | 124,000 | 730,000 | 14,000 | 14,000 | 190,000 | 1,100,000 | 20,000 | 20,000 |
| **Botanicals (Plant Alkaloids, 2,000 Metric Tons/Yr Plant Material)** | | | | | | | | | | | | |
| Wet Plant Material | 2,000 | 4,000 | – | – | 2,250 | 4,500 | – | – | 3,400 | 6,800 | – | – |
| Aqueous Solvent Concentrate | – | – | 720 | 850 | – | – | 810 | 960 | – | – | 1,200 | 1,400 |
| Halogenated Solvent | – | – | 60 | 60 | – | – | 70 | 70 | – | – | 100 | 100 |
| Non-Halogenated Solvent | – | – | 120 | 120 | – | – | 140 | 140 | – | – | 200 | 200 |
| Total for Plant Alkaloids | 2,000 | 4,000 | 900 | 1,030 | 2,250 | 4,500 | 1,020 | 1,170 | 3,400 | 6,800 | 1,400 | 1,700 |
| **Botanicals (Plant Steroids, 150 Metric Tons/Yr Stigmasterol)** | | | | | | | | | | | | |
| Fused Plant Steroid Ingots | 750 | 750 | – | – | 840 | 840 | – | – | 1,000 | 1,000 | – | – |

## TABLE 1.5 (Continued)

| Industry Segment | 1973 | | | | 1977 | | | | 1983 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | |
| | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† |
| **Medicinals from Animal Glands (8,000 Metric Tons Glands/Yr)** | | | | | | | | | | | | |
| Extracted Animal Tissue | 7,500 | 7,500 | – | – | 8,400 | 8,400 | – | – | 12,500 | 12,500 | – | – |
| Fats or Oils | 350 | 350 | – | – | 400 | 400 | – | – | 600 | 600 | – | – |
| Filter Cake (Containing protein) | 250 | 500 | – | – | 280 | 560 | – | – | 420 | 840 | – | – |
| Aqueous Solvent Concentrate | – | – | 800 | 1,600 | – | – | 900 | 1,800 | – | – | 1,350 | 2,700 |
| Total Medicinals from Animal Glands | 8,100 | 8,350 | 800 | 1,600 | 9,080 | 9,360 | 900 | 1,800 | 13,520 | 13,940 | 1,350 | 2,700 |
| Total for Production of Active Ingredients (SIC Code 2833) | 172,000 | 1,143,000 | 59,000 | 62,000 | 193,000 | 1,285,000 | 67,000 | 70,000 | 294,000 | 1,937,000 | 99,000 | 103,000 |
| **SIC Code 2831: Biological Products** | | | | | | | | | | | | |
| Aqueous Ethanol Waste from Blood Fractionation | – | – | 250 | 600 | – | – | 280 | 680 | – | – | 400 | 1,000 |
| Antiviral Vaccine | – | – | 300 | 300 | – | – | 350 | 350 | – | – | 500 | 500 |
| Other Biologicals | – | – | 200 | 200 | – | – | 225 | 225 | – | – | 350 | 350 |
| Total for Biological Products | – | – | 750 | 1,100 | – | – | 855 | 1,255 | – | – | 1,250 | 1,850 |
| **SIC Code 2834: Pharmaceutical Preparations** | | | | | | | | | | | | |
| Returned Goods | 10,000 | 10,000 | – | – | 11,300 | 11,300 | – | – | 17,000 | 17,000 | – | – |
| Contaminated or Decomposed Active Ingredient | – | – | 500 | 500 | – | – | 600 | 600 | – | – | 900 | 900 |
| | 10,000 | 10,000 | 500 | 500 | 11,300 | 11,300 | 600 | 600 | 17,000 | 17,000 | 900 | 900 |
| Totals for All Industry Segments | 181,850 | 1,153,000 | 61,650 | 65,100 | 204,300 | 1,836,300 | 70,445 | 73,755 | 311,000 | 1,954,000 | 103,850 | 108,450 |
| Rounded to: | 182,000 | 1,153,000 | 62,000 | 65,000 | 204,000 | 1,836,000 | 70,000 | 74,000 | 310,000 | 1,954,000 | 104,000 | 108,000 |

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*Source: Arthur D. Little, Inc., estimates.

†Wet weight estimates are given for all wastes. The two wastes that typically have the highest moisture content are biological sludge and mycelium from fermentations. Where the wet waste estimates are the same as on the dry basis, the waste is usually disposed of with only a minor amount of moisture. However, disposal practices vary from plant to plant, depending on the form in which the waste is produced.

## TABLE 1.6

## TECHNOLOGY LEVELS FOR DISPOSAL AND TREATMENT OF PHARMACEUTICAL INDUSTRY PROCESS WASTES[†]

| Industry Segment | Treatment and Disposal Technology<br>Level I | <br>Level II | <br>Level III |
|---|---|---|---|
| ● **R&D** | | | |
| Solvent | Incineration | → | → |
| Animals | Incineration | → | → |
| Heavy metals | Recovery | → | → |
| ● **Active Ingredient Production** | | | |
| – Organic Medicinal Chemicals | | | |
| Non-halogenated waste solvent | Incineration | → | → |
| Halogenated waste solvent | Incineration | → | → |
| High inert content wastes | | | |
| – containing flammables only | Landfill or incineration | Incineration | → |
| – containing heavy metals or corrosives | Landfill | Secure chemical landfill* | → |
| Heavy metal wastes | Secure chemical landfill** | Level I and recovery | Recovery and engineered storage |
| Organic chemical residues | Incineration | → | → |
| – Inorganic Medicinal Chemicals | | | |
| Heavy metal wastes | Chemical landfill*** | Secure chemical landfill*** | → |
| – Fermentation Products | | | |
| Waste solvent concentrate | Incineration | → | → |
| – Botanicals | | | |
| Aqueous solvent | Incineration | → | → |
| Halogenated waste solvent | Incineration | → | → |
| Non-halogenated waste solvent | Incineration | → | → |
| – Drugs from Animal Sources | | | |
| Aqueous alcohol | Incineration | → | → |
| – Biologicals | | | |
| Aqueous alcohol | Incineration | → | → |
| Antiviral vaccines | Incineration | → | → |
| Other biologicals (toxoids, serum) | Incineration | → | → |
| ● **Pharmaceutical Preparations** | | | |
| Returned goods and reject material | Landfill | Incineration | → |

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*Neutralize waste or precipitate heavy metal prior to placing in landfill.

**Convert heavy metal to most insoluble form and place in drum prior to placing in landfill.

***Waste is dilute; therefore, Level II technology will involve a more secure landfill rather than a recovery operation.

[†] **Source:** Arthur D. Little, Inc.

minimize or to change the hazardous nature of the wastes. More detailed analyses are given in Section 5.0. Table 1.7A and 1.7B summarize generalized costs of treatment and disposal systems either currently in use or recommended for future use in pharmaceutical production facilities. Because typical plants were used to develop an estimate of the total industry cost of treatment and disposal of hazardous wastes, the total industry costs should be taken only as an indication of the order of magnitude of such costs rather than as the outcome of a detailed industry survey of the costs. Issues such as site specific costs, different products or product mixes, local disposal rates, and available disposal methods were not included in this estimate.

### TABLE 1.7A

### PERSPECTIVES ON THE PHARMACEUTICAL INDUSTRY: HAZARDOUS WASTE TREATMENT AND DISPOSAL COSTS†

| | Total Annual Costs, $000** | | |
|---|---|---|---|
| | 1973 | 1977 | 1983 |
| **Product Category** | | | |
| ● Bulk Active Ingredient | | | |
| Organic Medicinal Chemicals | 3,800 | 4,295 | 6,140 |
| Inorganic Medicinal Chemicals* | – | – | – |
| Fermentation Products | 1,440 | 1,620 | 2,300 |
| Botanicals | 165 | 180 | 260 |
| Drugs from Animal Sources | 115 | 130 | 180 |
| Biologicals | 50 | 60 | 85 |
| ● Pharmaceutical Preparations | 15 | 40 | 50 |
| Partial Total+ | 5585 | 6325 | 9015 |

*One hazardous waste cost is included in organic medicinal chemicals.
**December 1973 dollars.
+Excludes R&D costs.

†**Source:** Arthur D. Little, Inc.

## TABLE 1.7B

## PERSPECTIVES ON THE PHARMACEUTICAL INDUSTRY: COST IMPACT OF HAZARDOUS WASTE TREATMENT AND DISPOSAL[†]

| Product Category | Price Level<br>$/kg | Estimated Hazardous Waste Control Cost as Percent of Price*<br>Level I | Level II | Level III |
|---|---|---|---|---|
| ● Bulk Active Ingredient | | | | |
| Organic Medicinal Chemicals | 22 | 0.2% | 0.22% | as Level II |
| Inorganic Medicinal Chemicals**/ | – | – | – | – |
| Fermentation Products | 44 | 0.34% | as Level I | as Level I |
| Botanicals | *** | < 0.1 | as Level I | as Level I |
| Drugs from Animal Sources | *** | | | |
| Biologicals | *** | | | |

* Manufacturers selling price in the case of pharmaceutical preparations; value of sales, that is, the net selling value FOB plant or warehouse, or delivered value, whichever represents the normal practice for bulk activity ingredient.

** Representative data not available because most inorganic medicinal ingredients that might produce a hazardous waste are purchased from the chemical industry.

*** Data not available; the selling price of many of these products is stated in terms of biological activity.

[†] Source: Arthur D. Little, Inc.

## 2.0 CHARACTERIZATION OF THE U.S. PHARMACEUTICAL INDUSTRY

### 2.1 CHARACTERIZATION OF THE INDUSTRY BY FUNCTION

The pharmaceutical industry can be described or characterized in several ways, depending on the needs of the particular study. For purposes of this report, we found it advantageous to break down the industry along functional lines in addition to classifying it by SIC codes.

The main function of the pharmaceutical industry is to provide delivery of active therapeutic substances in stable, useful dosage forms. Thus it may be distinguished from the chemical industry, the function of which is to synthesize various chemicals which may be useful in a variety of applications. It is true that the pharmaceutical industry may integrate vertically and become involved in the synthesis of active ingredients, but its major function is to prepare the tablets, injectables, ointments, capsules, and the like, to provide what is needed, where it is needed, and when it is needed.

The production and sale of pharmaceuticals may be outlined in a four-step series:

1. *Research and Development:* New drugs are discovered and developed by research laboratories (principally those of the pharmaceutical industry itself, but also those of government and educational institutions). After clinical trials and government approval, the drugs are ready for general production and sale.

2. *Production of Active Ingredients:* At this stage, the basic active drugs used in medicine are produced in bulk. These drugs can be categorized according to their principal ingredients as follows:

    a. organic medicinal chemicals (such as aspirin), inorganic medicinal chemicals (such as magnesium sulfate), fermentation products (such as penicillin and tetracycline), botanicals (such as quinine), and drugs from animal sources (such as insulin); and

    b. biological products, including vaccines (such as smallpox vaccine), toxoids (such as tetanus toxoid), serums (such as tetanus antitoxin), and products from human blood (such as plasma).

3. *Formulation and Packaging:* The basic drugs, which are manufactured in bulk, are formulated into various dosage forms such as tablets, ointments, syrups, lotions, injectable solutions, and the like, that can be taken by patients easily and in accurate amounts. The formulated products are packaged in appropriate containers.

4. *Pharmaceutical Marketing and Distribution:* To get the pharmaceuticals to doctors, hospitals, pharmacies, and ultimately to the patient or consumer, they are promoted by the pharmaceutical companies and distributed either directly by the companies or through wholesalers. Pharmaceuticals promoted by advertising directly to the consumer are called "proprietary pharmaceuticals" and those advertised to the medical, dental, and veterinary professions are called "ethical pharmaceuticals."

The larger, established pharmaceutical companies engage in all four functions – research, production, formulation, and marketing – although these may be carried out by separate divisions, often located many miles apart. Other companies, however, specialize in only one phase, such as producing medicinal chemicals in bulk or in formulating pharmaceutical products from purchased raw materials.

## 2.2 BREAKDOWN OF THE PHARMACEUTICAL INDUSTRY BY SIC CODES

The drug industry as defined by the U.S. Department of Commerce actually consists of three industries, consisting of producers of biological products, medicinal chemicals and botanical products, and pharmaceutical preparations. Under the 1972 SIC system, the three industry codes are assigned as follows:

- *SIC 2831–Biological Products:* Establishments primarily engaged in the production of bacterial and virus vaccines, toxoids and analogous products (such as allergenic extracts), serums, plasmas, and other blood derivatives for human and veterinary use.

- *SIC 2833–Medicinals and Botanicals:* Establishments primarily engaged in (1) manufacturing bulk organic and inorganic medicinal chemicals and their derivatives; and (2) processing (grading, grinding, and milling) bulk botanical drugs and herbs. Also included in the industry are establishments primarily engaged in manufacturing agar-agar and similar products of natural origin, endocrine products, manufacturing or isolating basic vitamins, and isolating active medicinal principals, such as alkaloids, from botanical drugs and herbs.

- *SIC 2834–Pharmaceutical Preparations:* Establishments primarily engaged in manufacturing, fabricating, or processing drugs in pharmaceutical preparations for human and veterinary use. Most of the products of these establishments are finished in the form intended for final consumption, such as ampuls, tablets, capsules, vials, ointments, medicinal powders, solutions, and suspensions. Products of this industry consist of two important lines, namely (1) pharmaceutical preparations promoted primarily to the dental, medical, or veterinary professions; and (2) pharmaceutical preparations promoted primarily to the public.

While there is no SIC code for Research and Development, the other SIC codes – 2831, 2833, and 2834 – can be fitted into the functional classification of the industry.

SIC 2834 (Pharmaceutical Preparations) is essentially the same as the Formulation and Packaging function described in Section 2.1.

SIC 2831 (Biological Products) has many manufacturing and isolation procedures similar to those in SIC 2833 (Medicinals and Botanicals). Therefore, for purposes of this study, we combined plant operations of both SIC 2831 and 2833 under Production of Active Ingredients.

## 2.3 DOMESTIC SALES OF THE U.S. PHARMACEUTICAL INDUSTRY

Total dollar volume of shipments for ethical products and proprietary products by the three sectors, according to Census Bureau figures, rose nearly 8% per year between 1954 and 1972, increasing from $2.05 to $7.54 billion, as shown in Table 2.3A.

**TABLE 2.3A**

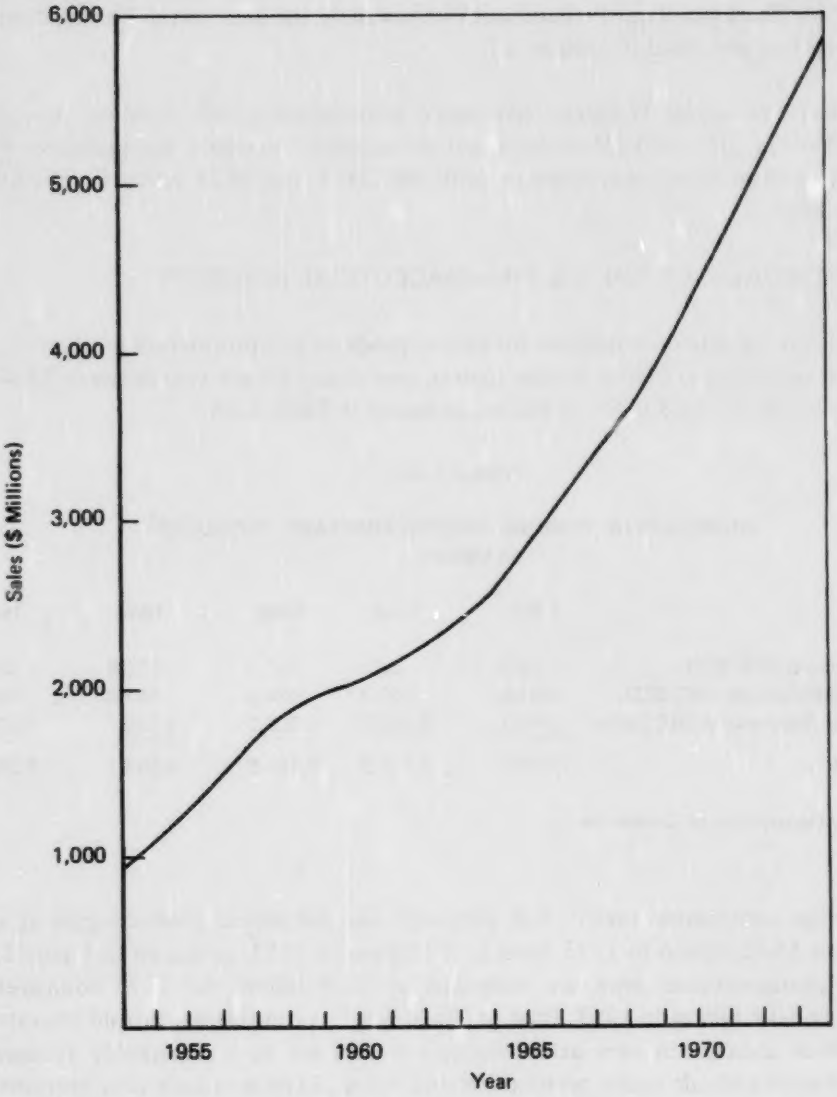
**SHIPMENTS OF ETHICAL AND PROPRIETARY PRODUCTS†**
**($ Millions)**

| | 1954 | 1958 | 1963 | 1967 | 1972 |
|---|---|---|---|---|---|
| Biological Products (SIC 2831) | 66.6 | 63.8 | 167.3 | 220.6 | 481.1 |
| Medicinals and Botanicals (SIC 2833) | 281.0 | 322.3 | 434.0 | 593.8 | 782.6 |
| Pharmaceutical Preparations (SIC 2834) | 1,700.5 | 2,591.8 | 3,000.2 | 4,139.7 | 6,276.0 |
| Total | 2,048.1 | 2,977.9 | 3,601.5 | 4,954.1 | 7,539.7 |

†**Source:** U.S. Department of Commerce

During the comparable period, U.S. domestic sales for ethical products grew at a 9% annual rate to $5.45 billion in 1973 from $1.00 billion in 1953, as shown in Figure 2.3A. Proprietary pharmaceutical sales are estimated at $1.9 billion for 1973 compared to approximately $0.4 billion in 1953. Prior to World War II, proprietaries outsold ethicals but the tremendous increase in new active ingredients has led to a remarkably accelerated growth of pharmaceuticals under prescription and other pharmaceuticals only promoted as ethicals. We expect ethical pharmaceuticals to continue to be the dominant factor in the expanded markets of the future.

Table 2.3B shows the estimated domestic sales of ethical pharmaceutical products and their growth rates by major therapeutic classes for selected years during the past decade. Within these major categories, the growth rates have varied substantially – from a slight decline in sulfonamides to a 19% growth for anti-arthritics. The most important factors stimulating demand during the period were:



[†] Source: Arthur D. Little, Inc., estimates.

FIGURE 2.3A ESTIMATED DOMESTIC SALES AT MANUFACTURERS' LEVEL OF ETHICAL PRODUCTS[†]

TABLE 2.3B

ESTIMATED DOMESTIC SALES* OF ETHICAL PHARMACEUTICAL PRODUCTS†
($ millions)

| Therapeutic Group | 1963 | 1967 | 1972 | 1973 | 1974** | Annual Growth Rate (%) From 1963 to 1973 |
|---|---|---|---|---|---|---|
| Analgesics | 90 | 160 | 270 | 292 | 310 | 12 |
| Antacids | 50 | 65 | 109 | 113 | 118 | 9 |
| Antiarthritics | 20 | 63 | 101 | 110 | 125 | 19 |
| Antibiotics | 363 | 458 | 697 | 730 | 760 | 7 |
| Antihistamines | 33 | 35 | 50 | 50 | 52 | 4 |
| Antiobesity Products | 65 | 82 | 67 | 71 | 80 | 1 |
| Antispasmodics | 53 | 70 | 89 | 92 | 97 | 6 |
| Ataraxics | 185 | 315 | 530 | 575 | 615 | 12 |
| Cardiovasculars | 110 | 200 | 348 | 387 | 425 | 13 |
| Cough and Cold Preparations | 80 | 125 | 198 | 223 | 250 | 11 |
| Diabetic Therapy | 72 | 99 | 127 | 130 | 140 | 6 |
| Diuretics | 65 | 96 | 174 | 200 | 225 | 12 |
| Hematinics | 36 | 36 | 42 | 41 | 43 | 1 |
| Hormones | 175 | 300 | 455 | 490 | 525 | 11 |
| Muscle Relaxants | 27 | 35 | 55 | 60 | 67 | 8 |
| Psychostimulants | 25 | 48 | 75 | 79 | 85 | 12 |
| Sedatives | 65 | 66 | 90 | 86 | 90 | 3 |
| Sulfonamides | 50 | 48 | 43 | 47 | 52 | 0 |
| Vitamins and Nutrients | 200 | 225 | 300 | 325 | 340 | 5 |
| Others | 619 | 840 | 1,230 | 1,349 | 1,411 | 8 |
| Total | 2,383 | 3,366 | 5,050 | 5,450 | 5,810 | 9 |

*At manufacturers' selling price.
**Preliminary estimates.

†Source: Arthur D. Little, Inc., estimates.

- The introduction of several important new drugs (e.g., Indocin [anti-arthritic], Lasix [diuretic], oral contraceptives, Valium and Librium [ataraxics]);

- Routine consumption of more drug products to control chronic illnesses and geriatric deterioration;

- New medical techniques and other health care products; and

- Continued growth in private and public health insurance.

At the present time, more than 1000 companies are considered as pharmaceutical firms because they sell drug products. Many are relatively small with annual sales less than $1 million and they frequently service a limited geographic area. Many do not manufacture their own products, but sell products to various drug outlets on a contract basis. They represent a small part of total drug sales. The distribution of pharmaceutical facilities by sales volume and geographical location is shown in Table 2.3C. Although sales data are not available for some firms (those in columns headed "G"), these firms usually are small and the numbers of facilities listed in columns headed "F" can be taken as indicative of the numbers of facilities with more than $10 million worth of annual sales. An inspection of the table indicates that only approximately 5 percent of the facilities in SIC codes 2831 and 2833 have sales greater than $10 million per year and only about 10 percent of the facilities in SIC code 2834 are of that size.

The Pharmaceutical Manufacturers Association (PMA) estimates that perhaps 600 to 700 U.S. firms actually produce ethical products. Many of these firms are quite small. In fact, the 110 members of the Pharmaceutical Manufacturers Association account for 95% of industry sales of ethical pharmaceuticals in this country. As shown in Figure 2.3B, this figure can be broken down with the top 15 companies accounting for greater than 50% of ethical sales and the top 40 companies accounting for 80% of domestic ethical sales. Moreover, since many drug companies function as a division of a larger corporation, the top 40 companies actually represent 33 corporations.

The evolving environment for pharmaceuticals suggests further concentration, with balanced resources in manufacturing, marketing, and research/development essential for successful participation in the expected growth. The industry leaders today possess the balanced resources necessary for success in the future. Because the barriers are substantial, probably few new pharmaceutical firms will be established.

## 2.4 HISTORICAL GROWTH OF THE U.S. PHARMACEUTICAL INDUSTRY

Historically, drug companies started as drugstores established to provide drugs to the public, but gradually they became more involved in preparing formulations for local physicians. The druggist ran a one-man show and acted as purchasing agent, production

# TABLE 2.3C

## FACILITIES BY SALES AND GEOGRAPHIC LOCATION†

| | | SIC 2831 Biologicals | | | | | | | SIC 2833 Medicinals and Botanicals | | | | | | | SIC 2834 Pharmaceutical Preparations | | | | | | | State Total | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A | B | C | D | E | F | G | A | B | C | D | E | F | G | A | B | C | D | E | F | G | A | B | C | D | E | F | G |
| IV | Alabama | 2 | | | | | | 3 | | | | | | | | 5 | 2 | | | | | 2 | 7 | 2 | | | | | 5 |
| X | Alaska | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| IX | Arizona | 1 | 2 | | | | | 2 | | 1 | | | | | | | 1 | 1 | 1 | | 1 | 4 | 1 | 4 | 1 | 1 | | 1 | 6 |
| VI | Arkansas | | | | | | | 1 | 1 | | | | | | | 2 | | | 1 | | | 3 | 3 | | | 1 | | | 4 |
| IX | California | 3 | 5 | 1 | 4 | 1 | 1 | 12 | 9 | 11 | 7 | 4 | 2 | 1 | 24 | 18 | 23 | 17 | 18 | 2 | 8 | 57 | 30 | 39 | 25 | 26 | 5 | 10 | 93 |
| VIII | Colorado | | 1 | 1 | 1 | | | 4 | 1 | | 1 | | | | 1 | | 1 | 3 | 1 | | | 6 | 1 | 2 | 5 | 2 | | | 11 |
| I | Connecticut | 1 | | | | | | | 1 | 4 | 1 | 3 | 1 | 2 | 4 | 5 | 6 | | 4 | | 2 | 5 | 7 | 10 | 1 | 7 | 1 | 4 | 9 |
| III | Delaware | | | | | | | 2 | | | | | | | 1 | | | | 2 | | 2 | 3 | | | | 2 | | 2 | 6 |
| III | District of Columbia | | | | | | | | | | | | | | | 2 | | | 1 | | | | 2 | | | 1 | | | |
| IV | Florida | | 3 | 1 | | | 1 | 3 | 3 | 3 | 1 | | | | 1 | 11 | 12 | | 9 | 1 | | 6 | 14 | 18 | 2 | 9 | 1 | 1 | 10 |
| IV | Georgia | 1 | 4 | 3 | | | | 2 | | | 1 | 1 | | | 4 | 7 | 5 | 1 | 3 | 1 | | 7 | 8 | 9 | 5 | 4 | 1 | | 13 |
| IX | Hawaii | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| X | Idaho | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| V | Illinois | 2 | 2 | | | 1 | | 10 | 4 | 7 | | 4 | 1 | | 26 | 15 | 20 | 8 | 17 | 2 | 7 | 34 | 21 | 29 | 8 | 21 | 4 | 7 | 70 |
| V | Indiana | | | | | | | 4 | 1 | 1 | | | | | 5 | 5 | 4 | 1 | 4 | | 3 | 9 | 6 | 5 | 1 | 4 | | 3 | 18 |
| VII | Iowa | | | 1 | 1 | 1 | | 1 | 1 | | | | | | 1 | 3 | 2 | 1 | 3 | | | 7 | 4 | 2 | 2 | 4 | 1 | | 9 |
| VII | Kansas | 1 | 3 | | 1 | | | 5 | 1 | 1 | | | | | | 1 | | | 4 | | | 4 | 3 | 4 | | 5 | | | 9 |
| IV | Kentucky | | 1 | | | | | | | | | | | | | 1 | 3 | 1 | | 1 | | 3 | 1 | 4 | 1 | | 1 | | 3 |
| VI | Louisiana | | | | | | | 1 | 1 | | | | | | 2 | 1 | 3 | | 2 | 1 | | 4 | 2 | 3 | | 2 | 1 | | 7 |
| I | Maine | | | | | | | 1 | | 2 | | | | 1 | 1 | | | | | | | | | 2 | | | | 1 | 2 |
| III | Maryland | 1 | 2 | | 1 | 2 | | 3 | 1 | 1 | 1 | | | | 1 | 3 | 6 | 2 | 2 | 1 | 1 | 3 | 5 | 9 | 3 | 3 | 3 | 1 | 7 |
| I | Massachusetts | 1 | | | 1 | | | 1 | 1 | 1 | | 1 | | | 1 | 14 | 6 | 3 | 2 | 1 | 2 | 8 | 16 | 9 | 3 | 4 | 1 | 2 | 10 |
| V | Michigan | | 1 | | | | 1 | 2 | 2 | 4 | | 1 | | 1 | 4 | 11 | 6 | 3 | 3 | 3 | 4 | 10 | 13 | 11 | 3 | 4 | 3 | 6 | 16 |
| V | Minnesota | | 1 | | 1 | | | | 1 | 2 | | | | | 1 | 5 | 6 | 1 | 2 | 1 | | 5 | 6 | 9 | 1 | 3 | 1 | | 6 |
| IV | Mississippi | | 1 | | | | | 1 | | 2 | | | | | | 2 | 3 | | | | | 7 | 2 | 6 | | | | | 8 |
| VII | Missouri | | | | | | 1 | 2 | 2 | 1 | 2 | | | 2 | 11 | 9 | 10 | 4 | 5 | | 3 | 24 | 11 | 11 | 6 | 5 | | 6 | 37 |
| VIII | Montana | 1 | | | | | | | | | | | | | | | | | | | | | 1 | | | | | | |
| VII | Nebraska | 1 | 1 | | 2 | | 1 | 1 | | | | 1 | | | | 1 | 2 | 1 | 2 | | | 6 | 2 | 3 | 1 | 5 | | 1 | 7 |
| IX | Nevada | | | | | | | | | | | | | | | | | | | | | 1 | | | | | | | 1 |
| I | New Hampshire | | | | | | | | 1 | | | | | | | 1 | | | | | | | 2 | | | | | | |
| II | New Jersey | | 3 | 2 | 2 | 1 | | 1 | 2 | 9 | 4 | 2 | 1 | 2 | 22 | 7 | 13 | 8 | 25 | 8 | 15 | 68 | 9 | 25 | 14 | 29 | 10 | 17 | 91 |
| VI | New Mexico | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| II | New York | 1 | 5 | 1 | 5 | | | 6 | 4 | 7 | 6 | 5 | 2 | 1 | 23 | 37 | 42 | 12 | 29 | 3 | 16 | 71 | 42 | 54 | 19 | 39 | 5 | 17 | 100 |
| IV | North Carolina | | 1 | | | 1 | | 1 | | 2 | | | | | 3 | 4 | 4 | 1 | 2 | | 1 | 10 | 4 | 7 | 1 | 2 | 1 | 1 | 14 |
| VIII | North Dakota | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| V | Ohio | 1 | | | 1 | | | | 4 | 1 | | | | | 3 | 13 | 5 | 3 | 1 | 1 | 2 | 14 | 18 | 6 | 3 | 2 | 1 | 2 | 17 |
| VI | Oklahoma | 1 | | | | | | 1 | | 3 | | | | | 1 | 1 | 2 | | 1 | | | 2 | 2 | 5 | | 1 | | | 4 |
| X | Oregon | | 1 | 1 | | | | | | | | 3 | | | 1 | 1 | 2 | 2 | 1 | | | 2 | 1 | 3 | 3 | 4 | | | 3 |
| III | Pennsylvania | 1 | 1 | 3 | | | | 4 | 1 | 6 | | | | | 11 | 14 | 14 | 6 | 10 | 5 | 7 | 24 | 16 | 21 | 9 | 10 | 5 | 7 | 39 |
| II | Puerto Rico | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| I | Rhode Island | | | | | 1 | | | | | | | | | 3 | | 2 | 1 | 1 | | | 1 | | 2 | 1 | 1 | 1 | | 4 |
| IV | South Carolina | | 1 | | | | | | | | | | | | 3 | 1 | 1 | | | | | 4 | 1 | 2 | | | | | 7 |
| VIII | South Dakota | | | | 1 | | | | | | | | | | | 1 | 1 | | | | | | 1 | 1 | | 1 | | | |
| IV | Tennessee | | | | | 1 | | 3 | | | | | | | 1 | 2 | 1 | | 3 | | 2 | 15 | 2 | 1 | | 3 | 1 | 2 | 19 |
| VI | Texas | 5 | 4 | | 2 | | | 8 | 5 | 7 | 1 | | | 1 | 6 | 11 | 10 | 5 | 7 | 1 | 1 | 20 | 21 | 21 | 6 | 9 | 1 | 2 | 34 |
| VIII | Utah | | | | | | | | 2 | | | | | | 1 | 2 | 1 | | | | | 1 | 4 | 1 | | | | | 2 |
| I | Vermont | | | | | | | | | | | | | | | | 2 | | | | | | | 2 | | | | | |
| III | Virginia | | 1 | | | | | | | | 1 | | | | 2 | 6 | 4 | 1 | | | 3 | 6 | 6 | 5 | 2 | | | 3 | 8 |
| X | Washington | 1 | | | 1 | | | 2 | | | | | | | | 5 | 3 | 1 | | | | 3 | 6 | 3 | 1 | 1 | | | 5 |
| III | West Virginia | | | | | | | | | | | | | | | | | | | | | 2 | | | | | | | 2 |
| V | Wisconsin | | 2 | | | | | 4 | 3 | 4 | | 2 | 1 | | 3 | 4 | 2 | 1 | 4 | | | 8 | 7 | 8 | 1 | 6 | 1 | | 15 |
| VIII | Wyoming | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | National Totals | 25 | 46 | 14 | 24 | 9 | 5 | 91 | 52 | 80 | 26 | 27 | 8 | 11 | 171 | 231 | 232 | 88 | 170 | 32 | 80 | 469 | 308 | 358 | 126 | 221 | 49 | 96 | 731 |
| | Region Totals | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | I | 2 | 0 | 0 | 1 | 1 | 0 | 2 | 3 | 7 | 1 | 4 | 1 | 3 | 9 | 20 | 18 | 4 | 7 | 1 | 4 | 14 | 26 | 25 | 5 | 12 | 3 | 7 | 25 |
| | II | 1 | 8 | 3 | 7 | 1 | 0 | 7 | 6 | 16 | 10 | 7 | 3 | 3 | 45 | 44 | 55 | 20 | 64 | 11 | 31 | 139 | 51 | 79 | 33 | 68 | 15 | 34 | 191 |
| | III | 2 | 4 | 3 | 1 | 2 | 0 | 9 | 2 | 7 | 2 | 0 | 0 | 0 | 15 | 26 | 24 | 9 | 16 | 6 | 13 | 38 | 29 | 35 | 14 | 16 | 8 | 13 | 62 |
| | IV | 3 | 11 | 4 | 0 | 2 | 1 | 13 | 3 | 7 | 2 | 1 | 0 | 0 | 12 | 33 | 31 | 3 | 17 | 3 | 3 | 54 | 39 | 49 | 9 | 18 | 5 | 4 | 79 |
| | V | 3 | 6 | 0 | 2 | 1 | 1 | 20 | 15 | 19 | 0 | 7 | 2 | 1 | 42 | 53 | 43 | 17 | 31 | 7 | 16 | 80 | 71 | 68 | 17 | 40 | 10 | 18 | 142 |
| | VI | 6 | 4 | 0 | 2 | 0 | 0 | 11 | 7 | 10 | 1 | 0 | 0 | 1 | 9 | 15 | 15 | 5 | 11 | 2 | 1 | 29 | 28 | 29 | 6 | 13 | 2 | 2 | 49 |
| | VII | 2 | 4 | 1 | 4 | 1 | 2 | 9 | 4 | 2 | 2 | 1 | 0 | 2 | 12 | 14 | 14 | 6 | 14 | 0 | 3 | 41 | 20 | 20 | 9 | 19 | 1 | 7 | 62 |
| | VIII | 1 | 1 | 1 | 2 | 0 | 0 | 4 | 3 | 0 | 1 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 1 | 0 | 0 | 7 | 7 | 4 | 5 | 3 | 0 | 0 | 13 |
| | IX | 4 | 7 | 1 | 4 | 1 | 1 | 14 | 9 | 12 | 7 | 4 | 2 | 1 | 24 | 18 | 24 | 18 | 19 | 2 | 9 | 62 | 31 | 43 | 26 | 27 | 5 | 11 | 100 |
| | X | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 6 | 5 | 3 | 1 | 0 | 0 | 5 | 7 | 6 | 4 | 5 | 0 | 0 | 8 |

| Key: | ($1,000) | | ($1,000,000) | |
|---|---|---|---|---|
| A | $ 0 – $ 99.9 | D | $ 1 – $4.9 |
| B | $100 – $499.9 | E | $ 5 – $9.9 |
| C | $500 – $999.9 | F | $10 – over |
| | | G | Not Available |

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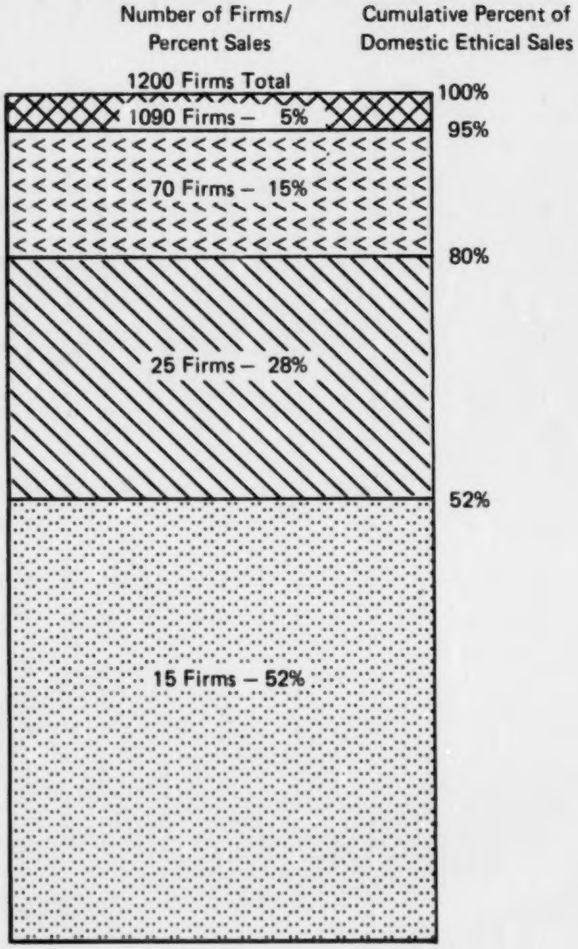
†Source: Arthur D. Little, Inc., estimates based on data from Dun & Bradstreet.



†**Source:** Arthur D. Little, Inc., estimates.

**FIGURE 2.3B INDUSTRY CONCENTRATION OF DOMESTIC ETHICAL SALES**†

superintendent, salesman, and treasurer. Traditionally, the drug operation was a family business, with the children taking an active role in the growing company. Because of this structure of strong family ties, most drug manufacturers were quite secretive about their businesses, and a strong relationship developed between the various companies. Several of the families developed significant businesses and began to employ professional managers to run their businesses profitably.

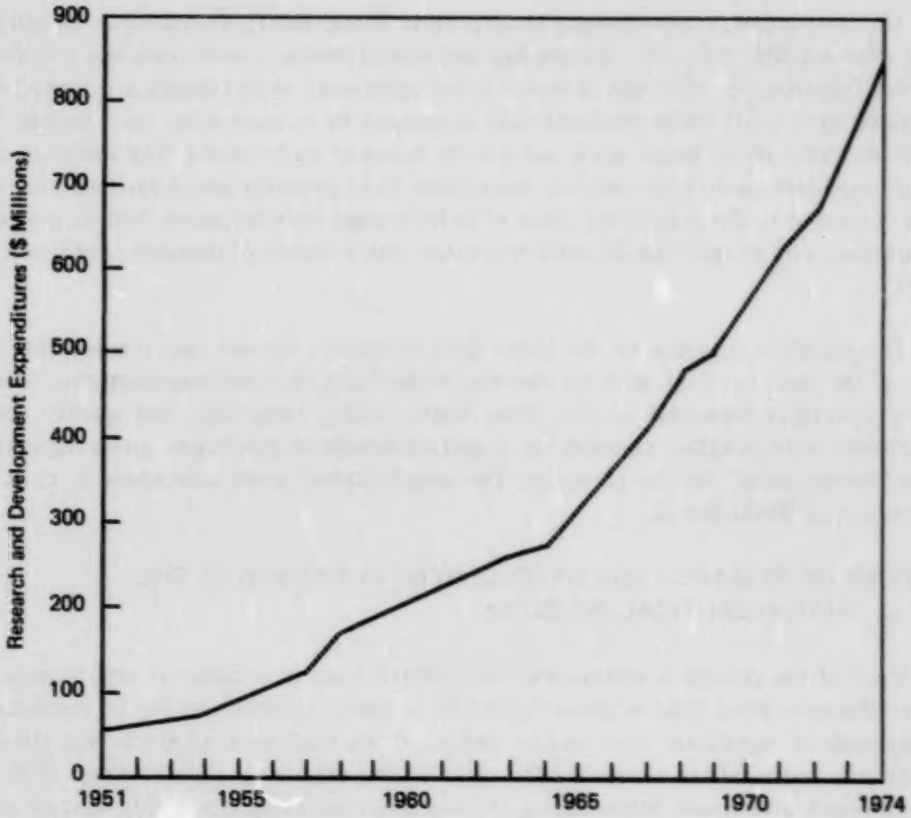
The drug industry was relatively small prior to World War II. Two distinct categories of drugs were available in 1939 – proprietary and ethical products, with proprietary outselling ethicals. Proprietaries were sold directly to the consumer, while ethicals were specified or prescribed by doctors. Most products were designated by a house label; for example, Lilly aspirin or Parke-Davis throat discs, and not by brand or trade names. The company name was an important part of the product description. Most products were relatively unsophisticated compared to those of today. Most of today's drugs were unknown, with rather simple preparations used to treat conditions now treated with a variety of complex, highly selective agents.

The principal activities of the larger drug companies did not vary considerably from those of the one-man shop, with the essential duties being sales and manufacturing. The size of the operation increased as the firms began selling nationally, and quality control laboratories were installed primarily to ensure standardized production and a high-quality image "house name" for the physician. The drug industry, as we now know it, came into existence after World War II.

## 2.5 ROLE OF RESEARCH AND DEVELOPMENT IN GROWTH OF THE U.S. PHARMACEUTICAL INDUSTRY

Much of the growth in ethical sales has resulted from new classes of compounds. The ethical pharmaceutical field is characterized by a heavy commitment to the research and development of significant new agents. Before 1950, traditional products like vitamins, barbiturates, and laxatives accounted for most of the industry's growth. After 1950, the heavy research investment begun during the war and continuing afterwards resulted in the new product explosion of antibiotics, steroids, and tranquilizers. The industry's emphasis on development of new products since then has produced an impressive array of effective products.

Figure 2.5 shows that the research and development (R&D) budget for the ethical drug industry has grown from $50 million in 1951 to $850 million in 1974. Traditionally, the ethical drug industry spends about 9-10% of its worldwide sales dollars on research effort – a higher percentage than in most other industries. Moreover, the R&D budget for specific companies may be substantially higher. For example, Lilly had worldwide pharmaceutical sales of $633.6 million in 1974, while its R&D spending was $93.3 million – nearly 15% of sales. Industry sources indicate the following partial analysis of expenditures:



†**Source:** Pharmaceutical Manufacturers Association.

**FIGURE 2.5 RESEARCH AND DEVELOPMENT EXPENDITURES FOR ETHICAL PRODUCTS*†**

*Government contract funds are not included nor is R&D funding for veterinary ethical products.

| | |
|---|---|
| Modifying and/or improving existing products | 29% |
| Biological screening and testing | 18 |
| Clinical testing | 17 |
| Synthesis and extraction | 16 |
| Process development, manufacturing work-up, and quality control | 10 |
| Toxicology and safety evaluation | 9 |
| | 99% |

In general, we believe that about one-sixth of the current industry-wide R&D budget is devoted to basic research and close to one-third to help existing products meet the FDA's more stringent requirements on bioavailability, efficacy, safety, and so forth. Thus, slightly more than one-half of the stated budget is devoted to new products.

In the past 30 years, almost 900 new active medicinal ingredients have been introduced to the U.S. market, two-thirds originating in the United States. (These active medicinal ingredients are unique compounds in terms of molecular structure. However, they may be used as an active ingredient in varying concentrations or in conjunction with other active ingredients in a number of different pharmaceutical products.) For the past decade, the number of new entities introduced annually into the U.S. market has tended to decline. In part, this decrease may be due to a trend in research to seek major breakthroughs for treatment of the more intractable diseases. However, the increased time needed for testing and meeting the FDA's regulatory requirements is an important factor. We estimate that the time factor can run five to eight years and cost from $9 to $18 million. Only the leading pharmaceutical companies have the money and research capacity needed to meet these demands.

Table 2.5 ranks published research activities on compounds by therapeutic categories to determine which research areas are currently of greatest interest. As future commercial production will depend in part on the areas now being researched, these data should give some indication of the future importance of various therapeutic classes. The 19 categories listed represent nearly 75% of all the compounds currently being investigated. The types of compounds under study suggest that there will be no drastic shift in the general types of active medicinal ingredients in the next 10 years, nor in the general processes (such as organic syntheses and fermentations) required to produce them.

R&D will be valued even more highly in the future, but it will also be more difficult to develop significant new agents. Much of the work which could lead quickly to drug discoveries has already been completed, and now investigators are concentrating on more difficult subjects, such as developing a basic understanding of heart disease, cancer, congenital disease, and stroke – all difficult areas in which to achieve quick developments. However, new breakthroughs in pharmacology will be forthcoming, involving not only new classes of therapeutic drugs but also advances brought about by molecular biology, that is, supplying missing or substitute chemicals in minute doses or in elaborate delivery systems in order to correct aberrant metabolism.

## TABLE 2.5

## RANKING OF RESEARCH CATEGORIES BY NUMBER OF COMPOUNDS UNDER STUDY[†]

| Category | Percent of Total Number of Compounds Under Study |
|---|---|
| Cardiovasculars | 14 |
| Psychotropic Drugs | 9 |
| Cancer Chemotherapy Agents | 6 |
| Antibiotics | 6 |
| Hormones | 4 |
| Antivirals | 3 |
| Analgesics | 3 |
| Antagonists/Antidotes | 3 |
| Muscle Relaxants | 3 |
| Anti-inflammatory Agents | 3 |
| Fungicides | 3 |
| Cholesterol Reducers | 2 |
| Enzyme Inhibitors | 2 |
| Diuretics | 2 |
| Bronchodilators | 2 |
| Antibacterials | 2 |
| Immunosuppressants | 2 |
| Anticoagulants | 2 |
| Antispasmodics | 2 |
| Others, each comprising less than 2% of the total compounds | 27 |

[†] **Sources:** Paul de Haen, Inc., and Arthur D. Little, Inc., estimates.

## 2.6 PHARMACEUTICAL CONSUMPTION – RECENT TRENDS

There is no simple unit of measure, such as millions of tablets or tons of chemicals, which shows overall unit consumption of pharmaceuticals. However, the trend of unit consumption can be inferred from the number of prescriptions filled at retail pharmacies.*

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* Retail pharmacies account for approximately 75% of all prescriptions, with hospitals and other institutions accounting for the balance.

Table 2.6 presents data on the number of prescriptions filled at retail pharmacies and shows that from 1968 to 1973, the number of prescriptions filled at retail pharmacies rose at a 6% compound annual rate to a total of 1.5 billion. New prescriptions rose at a somewhat higher rate of 6.4% and refill prescriptions grew at a 5.6% rate. The higher rate of growth in new prescriptions is primarily due to government restrictions on prescription refills for drugs that are subject to abuse, and above average growth in prescriptions for antibiotics. These data give a general indication of unit growth in drug consumption, but not a complete picture, because various drugs are taken with different frequencies and in different quantities. If anything, however, the growth rate is probably understated, since studies indicate that there has been an increase in the size of the average prescription in terms of numbers of tablets, capsules, and the like, per prescription.

## 2.7 PHARMACEUTICAL INDUSTRY OUTLOOK FOR 1975-1980

We expect the pharmaceutical industry to maintain a domestic dollar growth rate on the order of 7-9% over the next five years, and that international growth will probably be stronger in the near future. However, we believe that the production requirements of the industry will become more important as unit consumption increases. The following factors will be affecting the drug industry during this period:

- Enactment of an expanded program of National Health Insurance will be of prime importance during this period. We expect National Health Insurance to increase pharmaceutical sales and to boost drug consumption, particularly over the long-term, when coverage is extended to outpatient drugs. However, we do not anticipate legislation to be passed before 1976, with additional time required before the program can be implemented smoothly.

- Price pressures are being, and will continue to be, exerted by the Government. For example, HEW is currently assessing the maximum allowable cost regulations which would have an adverse impact on the profitability of the industry, particularly since the regulatory environment will encourage the use of price-competitive, multi-source drugs.

- Several Congressional hearings are being held which are investigating various practices of the pharmaceutical industry. For example, the Kennedy Health Subcommittee investigated many of the established marketing techniques of the industry, and we expect enforcement of related changes, particularly in the use of sampling and in the regulation of the activities of the medical representatives (detailmen). Such proposed curbs on promotional practices of drug companies could have a slightly adverse effect for a limited period of time.

- The availability of new drugs has slowed significantly from the flood of products introduced in the late 1950's and 1960's and is encouraging use of older, established drugs.

### TABLE 2.6

### NUMBER OF PRESCRIPTIONS FILLED AT RETAIL PHARMACIES[†]

| | Total Prescriptions | | New Prescriptions | | | Refill Prescriptions | |
|---|---|---|---|---|---|---|---|
| | Millions | Growth Rate % | Prescriptions | Millions | Growth Rate % | Millions | Growth Rate % |
| 1968-1973 | – | 6.0 | – | – | 6.4 | – | 5.6 |
| 1973 | 1532 | 5.7 | 48 | 729 | 4.7 | 803 | 6.5 |
| 1972 | 1450 | 7.3 | 48 | 696 | 7.7 | 754 | 6.8 |
| 1971 | 1351 | 5.5 | 48 | 646 | 7.1 | 706 | 4.4 |
| 1970 | 1280 | 6.9 | 47 | 603 | 7.3 | 676 | 6.5 |
| 1969 | 1197 | 4.5 | 47 | 562 | 5.2 | 635 | 3.8 |
| 1968 | 1145 | 7.1 | 47 | 534 | 8.5 | 612 | 6.1 |
| 1967 | 1069 | 1.3 | 46 | 492 | 3.4 | 577 | (0.4) |
| 1966 | 1055 | 9.1 | 45 | 476 | 10.2 | 579 | 8.2 |
| 1965 | 967 | 12.8 | 45 | 432 | 13.1 | 535 | 12.6 |
| 1964 | 857 | – | 44 | 382 | – | 475 | – |

[†] **Source:** National Prescription Audit

## 2.8 NUMBER OF PHARMACEUTICAL PLANTS AND EMPLOYMENT IN THE INDUSTRY

The latest available Census of Manufactures lists a total of 1058 establishments in 1972 for the SIC codes under evaluation. In addition, there were 42 plants in operation in Puerto Rico in 1974. Overall, a total of approximately 1100 plants are currently producing drug products in the United States and its territories. Most of these plants are small. Of the 1058 plants listed in the 1972 Census of Manufactures, in fact, only 416 had 20 or more employees each. For this study it is noteworthy that in the important function of producing organic chemical-active ingredients (SIC 2833), only 54 plants in the United States had 20 or more employees. Only 60 plants in the production of biologicals (SIC 2831) were in the comparable category and 302 were of this size in the formulation and packaging sector (SIC 2834).

Because Government data on a state-by-state basis were not complete at the time of this study, we have estimated the number of pharmaceutical plants in some of the States and Puerto Rico as shown in Table 2.8A. Totals of plants by EPA regions and for the individual states are presented on the map in Figure 2.8A. The corresponding map for plants with more than 100 employees is presented in Figure 2.8B. As may be observed in these tables and figures, drug industry production is concentrated primarily in the northeastern and north central regions, with relatively heavy involvement also in California. As designated by EPA regions, these include Regions II (282 plants – 26% of total), Region V (215 plants – 20% of total), and Region IX (143 plants – 13% of total). It should be noted that the new Puerto Rican facilities are incorporated into the total number of plants for Region II. For the continental United States, Region II contains 240 plants (22% of total).

A further indication of the geographic concentration of the U.S. pharmaceutical industry is the fact that five states have nearly 50% of all plants – New York (12%), California (12%), New Jersey (10%), Illinois (7%), and Pennsylvania (6%). Not only is the total number greater in these states, but the plants are also the largest in the industry. As shown in Figure 2.8B, these five states and Puerto Rico contain nearly two-thirds of the plants which have more then 100 employees.

An interesting observation from the Census data is that the total number of establishments in the continental United States dropped from 1359 facilities in 1958 to 1058 in 1972 (a decrease of 22%), but establishments with more than 20 employees increased from 403 to 416 during the same period (an increase of 3%). This shift is a further indication of the smaller producer disappearing from the industry with the larger manufacturers becoming even more dominant factors.

The number of employees in the various sections of the pharmaceutical industry from 1947 to 1972 are listed in Table 2.8B and presented graphically in Figure 2.8C. The industry employed a total of 129,300 workers in 1972, 67,400 of which were production workers. During the period 1958 to 1972, total employment increased by 26%, while production workers increased by 19%. This substantial increase in employment took place during the period noted above in which total plants decreased – again an indication of the concentration occurring within the industry.

## TABLE 2.8A

## ESTIMATED NUMBER OF PHARMACEUTICAL PLANTS (SIC 2831, 2833, AND 2834) TOTAL NUMBER OF PLANTS AND THOSE WITH MORE THAN 100 EMPLOYEES[†]

| EPA Region | State | Total Plants[1] | % of Total[2] | Plants @ >100 Employees | % of Plants[2] >100 Employees |
|---|---|---|---|---|---|
| IV | Alabama | ( 7) | * | 0 | 0 |
| X | Alaska | 0 | 0 | 0 | 0 |
| IX | Arizona | ( 8) | * | 0 | 0 |
| VI | Arkansas | ( 2) | * | 0 | 0 |
| IX | California | 134 | 12 | 18 | 8 |
| VIII | Colorado | ( 15) | 1 | 1 | * |
| I | Connecticut | 16 | 1 | 6 | 3 |
| III | Delaware | ( 4) | * | 0 | 0 |
| III | District of Columbia | 0 | 0 | 0 | 0 |
| IV | Florida | 28 | 3 | 1 | * |
| IV | Georgia | 18 | 2 | 3 | * |
| IX | Hawaii | 0 | 0 | 0 | 0 |
| X | Idaho | 0 | 0 | 0 | 0 |
| V | Illinois | 78 | 7 | 13 | 6 |
| V | Indiana | 26 | 2 | 9 | 4 |
| VII | Iowa | 16 | 1 | 3 | 1 |
| VII | Kansas | 12 | 1 | 1 | * |
| IV | Kentucky | ( 5) | * | 0 | 0 |
| VI | Louisiana | ( 11) | 1 | 0 | 0 |
| I | Maine | ( 3) | * | 0 | 0 |
| III | Maryland | 23 | 2 | 2 | * |
| I | Massachusetts | 31 | 3 | 2 | * |
| V | Michigan | 39 | 4 | 10 | 5 |
| V | Minnesota | ( 21) | 2 | 2 | * |
| IV | Mississippi | ( 8) | * | 1 | * |
| VII | Missouri | 44 | 4 | 10 | 5 |
| VIII | Montana | 0 | 0 | 0 | 0 |
| VII | Nebraska | 9 | * | 2 | * |
| IX | Nevada | ( 1) | * | 0 | 0 |
| I | New Hampshire | 0 | 0 | 0 | 0 |
| II | New Jersey | 112 | 10 | 45 | 21 |
| VI | New Mexico | 0 | 0 | 0 | 0 |
| II | New York | 128 | 12 | 26 | 12 |
| IV | North Carolina | ( 18) | 2 | 5 | 2 |
| VIII | North Dakota | 0 | 0 | 0 | 0 |
| V | Ohio | 34 | 3 | 5 | 2 |
| VI | Oklahoma | ( 5) | * | 0 | 0 |
| X | Oregon | ( 9) | * | 1 | * |
| III | Pennsylvania | 69 | 6 | 19 | 9 |
| II | Puerto Rico | 42 | 4 | 16 | 7 |
| I | Rhode Island | ( 4) | * | 0 | 0 |
| IV | South Carolina | ( 6) | * | 2 | * |
| VIII | South Dakota | ( 2) | * | 0 | 0 |

### TABLE 2.8A (Continued)

| EPA Region | State | Total Plants[1] | % of Total[2] | Plants @ >100 Employees | % of Plants[2] >100 Employees |
|---|---|---|---|---|---|
| IV | Tennessee | 16 | 1 | 7 | 3 |
| VI | Texas | 50 | 5 | 4 | 2 |
| VIII | Utah | ( 3) | * | 1 | * |
| I | Vermont | 0 | 0 | 0 | 0 |
| III | Virginia | ( 16) | 1 | 3 | 1 |
| X | Washington | ( 7) | * | 0 | * |
| III | West Virginia | ( 3) | * | 0 | * |
| V | Wisconsin | 17 | 2 | 1 | * |
| VIII | Wyoming | 0 | 0 | 0 | * |
| | National Totals | 1100 | | 219 | |
| | Regional Totals | | | | |
| | I | 54 | 5 | 8 | 4 |
| | II | 282 | 26 | 87 | 40 |
| | III | 115 | 10 | 24 | 11 |
| | IV | 106 | 10 | 19 | 9 |
| | V | 215 | 20 | 40 | 18 |
| | VI | 68 | 6 | 4 | 2 |
| | VII | 81 | 7 | 16 | 7 |
| | VIII | 20 | 2 | 2 | * |
| | IX | 143 | 13 | 18 | 8 |
| | X | 16 | 1 | 1 | * |

1. Figures in parentheses are Arthur D. Little, Inc., estimates, based on 1967 Census of Manufactures and Dun and Bradstreet 1974 data; all others from 1972 Census of Manufactures (Preliminary).
2. *designates less than 1%.

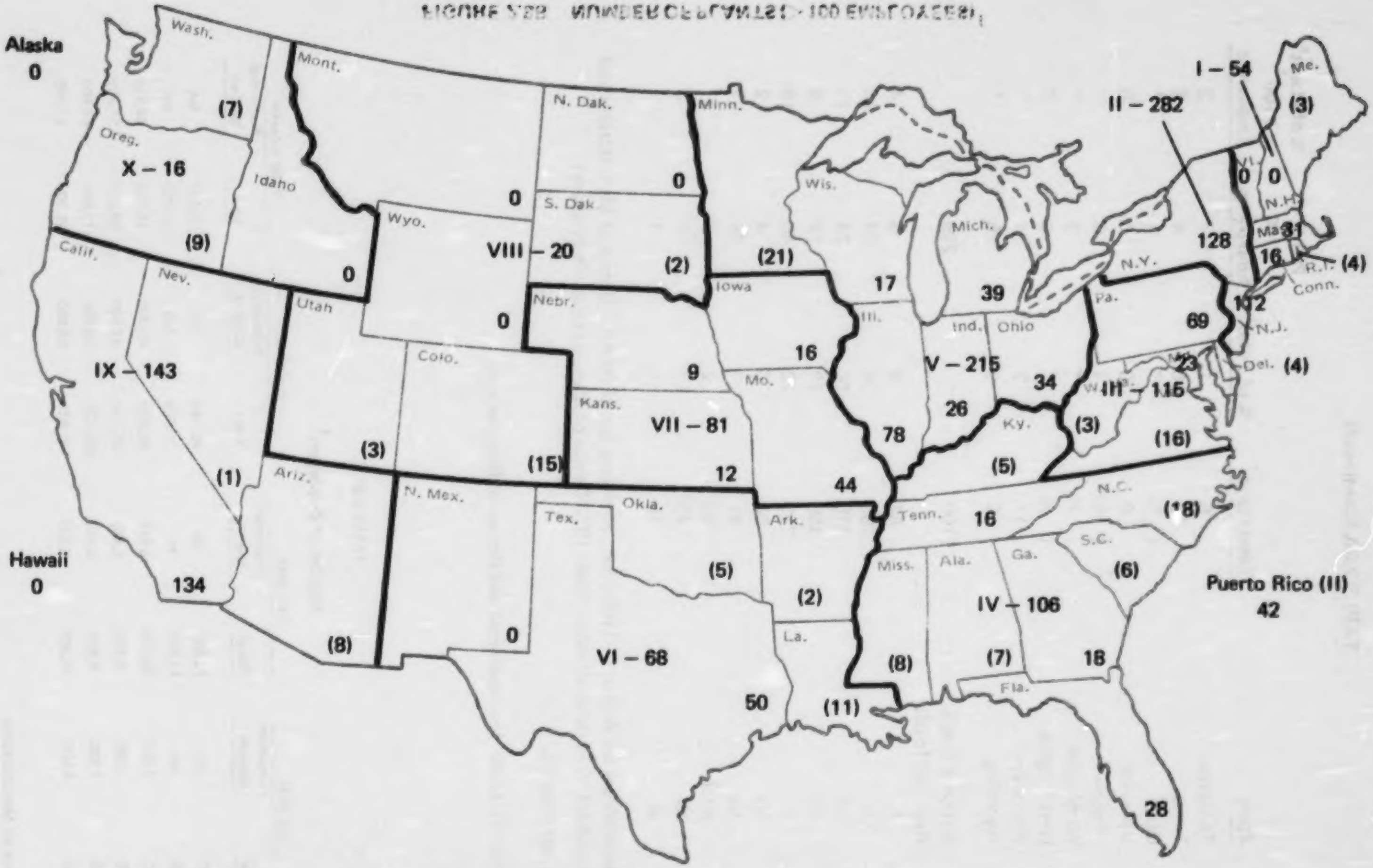
†Sources: Arthur D. Little, Inc., estimates and Census of Manufactures.

### TABLE 2.8B

Number of Employees†

| | SIC 2831 | | SIC 2833 | | SIC 2834 | | Total Industry | |
|---|---|---|---|---|---|---|---|---|
| | Total | Production Workers | Total | Production Workers | Total | Production Workers | Total | Production Workers |
| 1947 | 2,987 | NA | 13,097 | NA | 65,143 | NA | 81,227 | NA |
| 1954 | 3,965 | NA | 11,541 | NA | 76,555 | NA | 92,061 | NA |
| 1958 | 3,692 | 2,567 | 10,246 | 6,640 | 82,000 | 45,708 | 95,938 | 54,915 |
| 1963 | 5,800 | 3,600 | 8,100 | 5,300 | 85,100 | 45,900 | 99,000 | 54,800 |
| 1967 | 7,400 | 4,800 | 8,400 | 5,600 | 102,000 | 55,200 | 117,800 | 65,600 |
| 1972 | 9,800 | 5,500 | 8,700 | 5,300 | 110,800 | 56,600 | 129,300 | 67,400 |

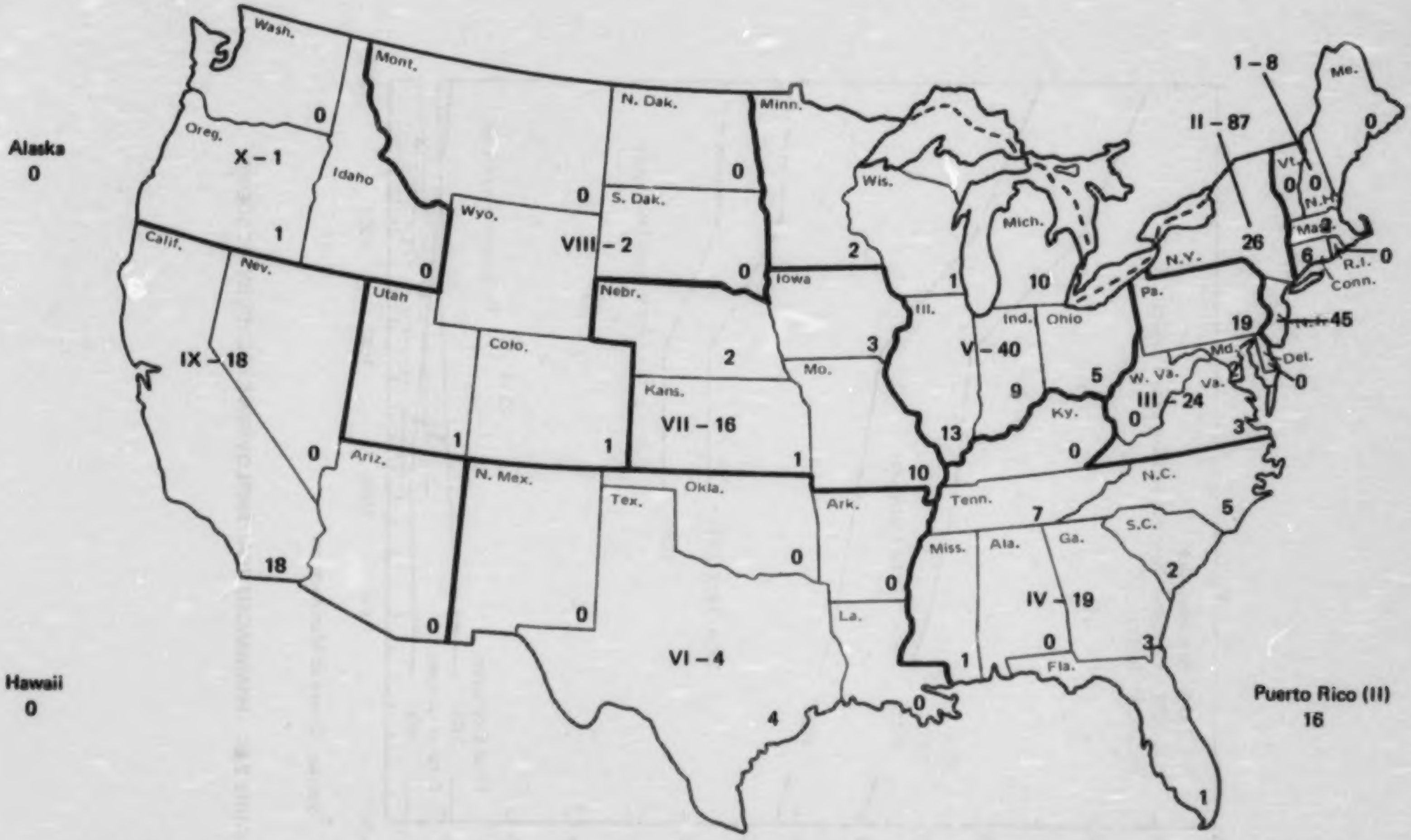
†Source: Census of Manufactures


Alaska
0
Hawaii
0
Puerto Rico (II)
42
Wash.
(7)
Oreg.
X – 16
(9)
Idaho
0
Mont.
0
Wyo.
VIII – 20
0
N. Dak.
0
S. Dak.
(2)
Calif.
Nev.
IX – 143
(1)
134
Utah
(3)
Colo.
(15)
Ariz.
(8)
N. Mex.
0
Nebr.
9
Kans.
VII – 81
12
Iowa
16
Mo.
44
Minn.
(21)
Tex.
Okla.
(5)
VI – 68
50
Ark.
(2)
La.
(11)
Wis.
17
Ill.
78
Mich.
39
Ind.
Ohio
V – 215
26
34
Ky.
(5)
Tenn.
16
Miss.
(8)
Ala.
(7)
Ga.
IV – 106
18
Fla.
28
S.C.
(6)
N.C.
(18)
W. Va.
(3)
III – 115
(16)
Md.
23
Del.
(4)
Pa.
69
N.Y.
128
N.J.
112
II – 282
I – 54
Vt.
0
N.H.
0
Me.
(3)
Mass.
31
16
R.I.
(4)
Conn.

N.B.: Numbers in parentheses are Arthur D. Little, Inc., estimates; Roman numerals designate EPA regions.

[†]Sources: Arthur D. Little, Inc., estimates and Census of Manufactures, 1972 (preliminary).

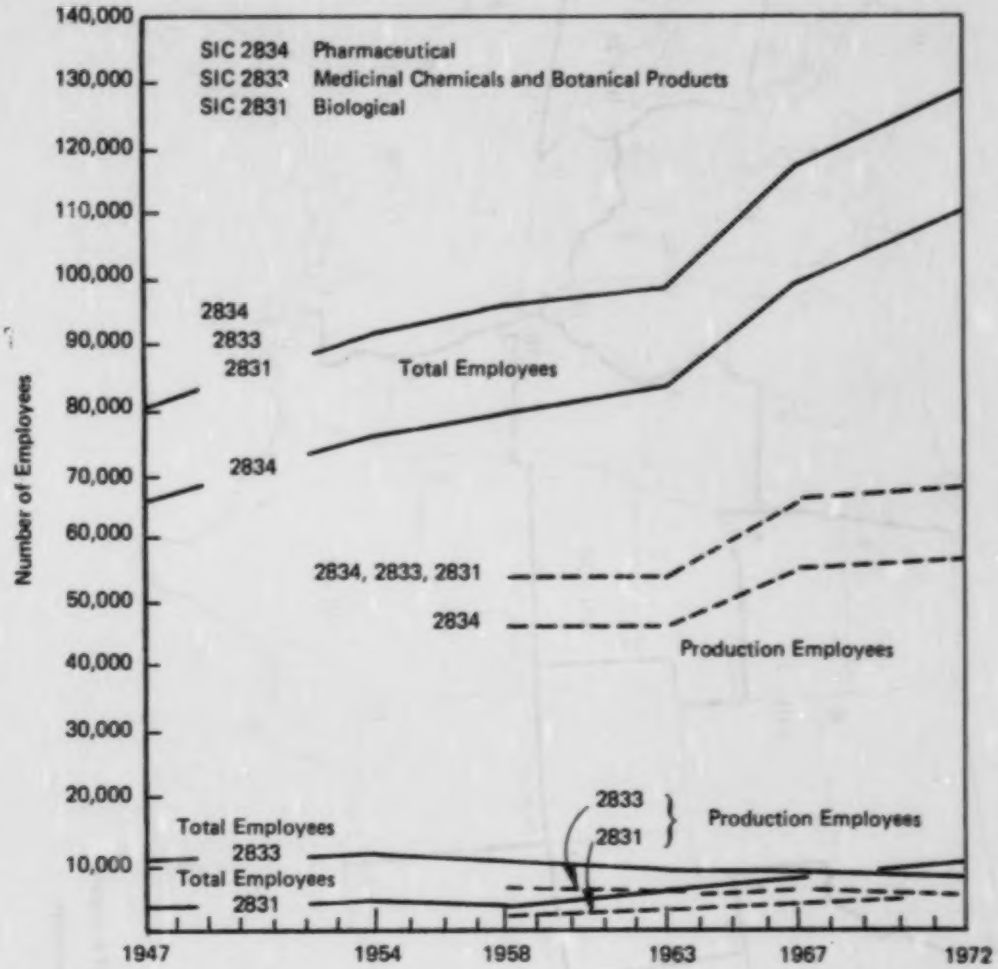
FIGURE 2.8A NUMBER OF PLANTS[†]


Alaska
0
Hawaii
0
Puerto Rico (II)
16
X – 1
IX – 18
VIII – 2
VII – 16
VI – 4
V – 40
IV – 19
III – 24
II – 87
1 – 8
Wash.
Oreg.
Idaho
Calif.
Nev.
Mont.
Wyo.
Utah
Colo.
Ariz.
N. Mex.
N. Dak.
S. Dak.
Nebr.
Kans.
Okla.
Tex.
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ind.
Ohio
Ky.
Tenn.
Miss.
Ala.
Ga.
Fla.
S.C.
N.C.
Va.
W. Va.
Md.
Del.
Pa.
N.Y.
N.J.
Conn.
R.I.
Mass.
Vt.
N.H.
Me.

N.B.: Roman numerals designate EPA regions.

†Source: Arthur D. Little, Inc., estimates.

FIGURE 2.8B NUMBER OF PLANTS (> 100 EMPLOYEES)†



†Source: Census of Manufactures

FIGURE 2.8C PHARMACEUTICAL EMPLOYMENT TRENDS BY SIC CODES†

# 3.0 WASTE CHARACTERIZATION IN THE PHARMACEUTICAL INDUSTRY

## 3.1 SELECTION AND APPLICATION OF HAZARDOUS WASTE CRITERIA

### 3.1.1 Background Information for the Selection of Hazardous Wastes

In the studies covering various industries, the individual contractors were asked to:

> *". . . identify and describe the wastes generated by each industry which pose a potential health or environmental hazard upon final disposal. In performing his analysis, the contractor should pay particular attention to wastes which contain any of the following specific substances, or types of substances: asbestos, arsenic, beryllium, cadmium, chromium, copper, cyanides, lead, mercury, halogenated hydrocarbons, pesticides, selenium, and zinc. EPA believes these substances, on the basis of initial analysis, to have the potential for producing serious public health and environmental problems when contained in wastes for disposal. Other wastes, believed by the contractor to be of a hazardous nature, such as carcinogens, should also be identified."*

To identify the wastes that pose a potential health or environmental hazard upon final disposal, we had to develop a set of criteria to select the hazardous wastes generated by the pharmaceutical industry. Whereas some industries have only a few well defined inorganic substances to classify, the pharmaceutical industry manufactures or purchases an estimated 15,000 inorganic and organic chemicals to make its formulated pharmaceutical products. Potential hazards of these chemicals range from essentially nonhazardous to highly hazardous due to such characteristics as flammability or toxicity.

We studied other hazard classification schemes to assist in developing criteria for selecting potentially hazardous and highly hazardous wastes generated in the pharmaceutical industry, but found no universally applicable scheme for classifying the types of hazards and the degree to which they are hazardous. Each classification scheme was selected to meet specific needs. Industrial toxicologists selected criteria to assist them in handling the toxic materials produced in industry, and public health toxicologists assembled criteria to assist the physician in treating acute poisoning by various chemicals and commercial products. Classification schemes designed to aid the physician in treating acute poisonings were usually developed on the basis of $LD_{50}$ values alone, while the industrial hygienist was often more concerned with the toxicity of inhaled vapors, irritation to the skin, allergic reactions, and flammability of products.

While none of the other systems have addressed the same problems that the Office of Solid Waste Management Programs will face, the Coast Guard addressed a related problem in the safe handling of materials in bulk water transportation. During 1965-66 the National

Academy of Sciences (NAS) developed an initial evaluation system for the Coast Guard.* In this system the substances were rated on a simple numerical scale of 0, 1, 2, 3 or 4, indicating an increasing degree of hazard in each of 10 categories describing different types of hazards (flammability, human toxicity, etc.). The publication was revised from time to time; the current edition is dated 1970 with additions to September 22, 1972. Comments were received from overseas sources including the Intergovernmental Maritime Consultative Organization (IMCO), the Netherlands, and the United Kingdom, suggesting the need for further extension and amplification of the guidelines to define the ratings more precisely. Thus in 1974 the NAS submitted a revised publication, "System for Evaluation of the Hazards of Bulk Water Transportation of Industrial Chemicals," which brought the grade classifications for human toxicity and aquatic toxicity into agreement with grade classifications developed by IMCO and one hazard category (effect on amenities) was dropped. The suggested classification scheme now has nine hazard categories as follows: (1) fire, (2) skin and eyes, (3) vapor inhalation, (4) gas inhalation, (5) repeated inhalation, (6) human toxicity, (7) aquatic toxicity, (8) water reaction, and (9) self reaction. The same rating scale of 0, 1, 2, 3 and 4 was retained and used for all hazard categories.

We also examined the IMCO system which was developed by the Joint Group of Experts on the Scientific Aspects of Marine Pollution to review the environmental hazards of transporting substances besides oil. In contrast to the NAS system which has nine categories of hazards, the IMCO system has only five categories: (1) bio-accumulation, (2) damage to living resources, (3) oral intake hazard to human health, (4) skin contact and inhalation hazard to human health, and (5) reduction of amenities.

### 3.1.2 Selection of Criteria for Classification of Potentially Hazardous Substances from the Pharmaceutical Industry

Classification of materials as hazardous or nonhazardous is an arbitrary process. Whether or not a substance is hazardous depends on its quantity, concentration, location, and the species affected. Even air and water can be hazardous in certain situations. For example, air injected into a vein may cause a fatal air embolism. Likewise water can be fatal if too much water gets into the lungs by blocking access of air to the lungs and seriously disrupting the ionic balance of the blood. On the other hand, a substance such as hydrochloric acid, which can be fatal if ingested in concentrated form, can also be beneficial in dilute solutions for patients who have a deficiency of normal hydrochloric acid secretions in the stomach.

Despite the difficulties of developing a universally applicable scheme for grading hazardous materials, materials with the highest potential for environmental damage and human hazard can be identified for various handling or disposal techniques. Theoretically, such a classification scheme should take in all possible hazards. In observing the pragmatic approaches taken by IMCO, NAS-Coast Guard, and the Hazardous Substances Branch of EPA's Office of Water Planning and Standards, it is apparent that firm decisions had to be made to eliminate or exclude certain hazard categories. For example, effects on amenities was eliminated in the 1974 NAS proposed system and bio-accumulation was not included as a hazard category. Likewise, the IMCO scheme did not include consideration of flammability in its hazard ratings, presumably because it is concerned with dumping of materials from ships on the high seas where toxicity is a more important consideration than flammability.

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*Described in NAS publication No. 1465, "Evaluation of the Hazard of Bulk Water Transportation of Industrial Chemicals – A Tentative Guide."

Because of the wide range of hazards considered in the NAS scheme, and because of the extensive data that had been collected for the scheme, we proposed that the 1974 modification suggested to the Coast Guard by NAS be used as a basis for evaluating the hazards of materials for disposal on land. Initially, we suggested classifying substances which fell into hazard grades 3 and 4 in any category of the NAS scheme as highly hazardous and those in grades 1 and 2 as moderately hazardous as shown in Table 3.1.2A. Another contractor (TRW, Inc.) suggested expansion of the NAS-Coast Guard classification to include bio-accumulation to toxic levels and addition of substances that are carcinogenic, oncogenic, teratogenic, or mutagenic. Since the classification scheme developed for this preliminary study of hazardous wastes would not bind EPA to the same criteria, the Office of Solid Waste Management Programs, ADL, and TRW agreed that both contractors would use the expanded classification scheme for the pharmaceutical and organic chemical industries, but with a modification involving the water pollution hazards. The criteria for highly hazardous wastes were retained and, therefore, included any substances falling into hazard grades 3 or 4 in any category of the NAS classification scheme. Criteria for moderately hazardous wastes included any substance falling in grades 1 or 2 in any category, except that under the "water pollution" heading substances falling in grade 1 were considered nonhazardous unless they presented a hazard upon collection. We thus have nine graded criteria to use in making preliminary judgments in evaluating the hazard of a given material. In addition, bio-concentratable materials are raised to the next higher hazard classification and suspected carcinogens* are rated as Grade 4, highly hazardous. A summary of the classification criteria is presented in Table 3.1.2A with the boundaries between the three hazard classifications (highly hazardous, moderately hazardous, and essentially nonhazardous) delineated by heavy lines. A more detailed explanation of the criteria for hazard grades in each of the nine categories is given in Appendix A.

When one attempts to apply the classification scheme developed above to a specific industrial situation, other precautions must be observed. The problems of quantity and concentration arise immediately when we consider the inorganic chemicals (heavy metals and fluorides, for example) that are usually considered to be toxic. The assumption that any exposure to a toxic chemical is harmful at any dose is erroneous; for many chemical substances a deficiency is known to be every bit as injurious as an excess.

Several examples illustrate that substances can be nutritional at one level and toxic at another. For example, fluorine is essential for life (Table 3.1.2B) and is a demonstrated growth factor in rats. A fluorine deficiency leads to tooth decay, but in slight excess this

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*Does not include list of "suspected carcinogens" published by NIOSH in the Federal Register, *48*, No. 121, pp 26,390-26,496, June 23, 1975. NIOSH is asking for information on the carcinogenicity of compounds on this list.

## TABLE 3.1.2A

## SUMMARY OF HAZARD EVALUATION CRITERIA

|  |  | Hazard Categories |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | GRADE | I | II | III | IV | V | VI | VII | VIII | IX |
|  |  | Fire | Health |  |  |  | Water Pollution |  | Reaction |  |
|  |  |  | Skin and Eyes | Vapor Inhalation | Gas Inhalation | Repeated Inhalation | Human Toxicity | Aquatic Toxicity | Water Reaction | Self-Reaction |
| Essentially Nonhazardous Wastes | 0 | Non-combustible | All not described below | All not described below | Not Applicable | OSHA > 1000 ppm | $LD_{50}$ > 5000 mg/kg | Insignif. Hazard<br>$TL_m > 1000$ mg/ℓ |  | No appreciable self-reaction |
| Priority II Moderately Hazardous Wastes | 1 | FPcc > 140°F (60°C) | Corrosive to eyes | Depressants, asphyxiants | All not described below | OSHA 100-1000 ppm | $LD_{50}$ 500-5000 mg/kg | $TL_m$ 100-1000 mg/ℓ | e.g., $Cl_2$ | May polymerize with low heat evolution |
|  | 2 | FPcc 100°F-140°F (37.8°-60°C) | Corrosive to skin | $LC_{50}$ 200-2000 ppm | $LC_{50}$ 200-2000 ppm | OSHA 10-100 ppm | $LD_{50}$ 50-500 mg/kg | $TL_m$ 10-100 mg/ℓ | e.g., $NH_3$ | Contamination may cause polymerization; no inhibitor required |
| Priority I* Highly Hazardous Wastes | 3 | (37.8°C) FPcc < 100°F BP > 100°F (37.8°C) | $LD_{50}$ 20-200 mg/kg 24-hr. skin contact | $LC_{50}$ 50-200 ppm or 0.5-2 mg/ℓ | $LC_{50}$ 50-200 ppm | OSHA 1-10 ppm | $LD_{50}$ 5-50 mg/kg | $TL_m$ 1-10 mg/ℓ | e.g., Oleum | May polymerize; requires stabilizer |
|  | 4 | (37.8°C) FPcc < 100°F BP < 100°F (37.8°C) | $LD_{50} \leq 20$ mg 24-hr. skin contact | $LC_{50} \leq 50$ ppm or $\leq 0.5$ mg/ℓ | $LC_{50} \leq 50$ ppm | OSHA < 1 ppm | $LD_{50} < 5$ mg/kg | $TL_m < 1$ mg/ℓ | e.g., $SO_3$ | Self-reaction may cause explosion or detonation |

*Priorities are discussed in Subsection 3.1.3

**Note:** Bio-concentratable materials are raised to next higher hazard classification. Suspected carcinogens are rated as Grade 4.

## TABLE 3.1.2B

## BIOLOGICAL FUNCTIONS AND TOXICITIES OF SELECTED ELEMENTS

| Element | Biological Function* | Toxicity** |
|---|---|---|
| Hydrogen | Constituent of water and organic compounds | |
| Boron | Essential in some plants; function unknown | |
| Carbon | Constituent of organic compounds | |
| Nitrogen | Constituent of many organic compounds | |
| Oxygen | Constituent of water and organic compounds | |
| Fluorine | Growth factor in rats; possible constituent of teeth and bones | Used in insecticides and rat poisons; fluorides are protoplasmic poisons, removing essential body calcium interfering with enzyme reactions causing death from respiratory or cardiac failure |
| Sodium | Principal extracellular cation | |
| Magnesium | Required for activity of many enzymes | High plasma levels can result in respiratory depression and death |
| Silicon | Shown essential in chicks; possible structural unit in diatoms | |
| Phosphorus | Essential for biochemical synthesis and energy transfer | |
| Sulfur | Required for proteins and other biological compounds | |
| Chlorine | Principal extracellular anion | |
| Potassium | Principal cellular cation | |
| Calcium | Major component of bone; required by some enzymes | |
| Vanadium | Essential in lower plants; certain marine animals and rats | Quite toxic, especially as $V_2O_5$ dust |
| Chromium | Essential in higher animals; related to action of insulin | Carcinogenic in rats and mice; industrial exposure has resulted in dermatitis, skin ulcers, liver injury, and lung cancer. |
| Manganese | Required for activity of several enzymes | Industrial exposure to dust has resulted in a neurological syndrome and a pneumonitis |
| Iron | Most important transition metal ion essential for hemoglobin and many enzymes | Excessive doses have caused severe symptoms and a high proportion of deaths, especially in children; acidosis, cardiovascular collapse and tissue damage to the gastro-intestinal tract, liver and kidneys |
| Cobalt | Required for activity of several enzymes; in vitamin $B_{12}$ | Produces polycythemia, nephritis, etc. |
| Copper | Essential in oxidative and other enzymes and hemocyanin | Excessive doses damage liver, kidneys, capillaries, and central nervous systems |
| Zinc | Required for activity of many enzymes; deficiency causes anemia | Relatively nontoxic to mammals; yet causes illness due to inhalation of Zn compounds |
| Selenium | Essential for liver function | High toxicity, similar to Te and As; Even natural levels cause serious disease (blind staggers) in cattle; inhibits enzyme function |
| Molybdenum | Required for activity of several enzymes | |
| Tin | Essential in rats; function unknown | |
| Iodine | Essential constituent of thyroid hormones | Iodism in some persons; irritation of mucous membranes and gastro-intestinal tract |

*from E. Frieden, *Scientific American, Vol 227,* No. 1, p 52 (July 1972).

**from J.R. DiPalma (ed.), *Drill's Pharmacology in Medicine,* (3rd ed.), McGraw-Hill Book Co., New York (1965).

same element produces an unsightly mottling of tooth enamel. In large excess it is a very dangerous poison – the active ingredient, in fact, in some insecticides and rat poisons.

Another example is zinc. Many enzymes require this element yet it can be an industrial health hazard and has been responsible for fish kills. The list of chemical elements essential to life is growing fast. It includes eight other "toxic heavy metals" – vanadium, chromium, manganese, iron, cobalt, copper, molybdenum, and tin – which were listed by Frieden in 1972 (cf. Table 3.1.2B).

### 3.1.3 Application of the Classification Scheme to Categorize Wastes from the Pharmaceutical Industry as Priority I or Priority II Potentially Hazardous Wastes

As was discussed in Section 3.1.2, the toxicity or degree of hazard presented by a given waste depends on many factors. In this preliminary survey of hazardous wastes from the pharmaceutical industry potentially destined for land disposal, we were unable to make final judgments on the degree of "hazard" for wastes from the industry. We recognize that more information will be required on a plant by plant basis before the hazards at an individual plant can be evaluated. In this report, we have focused on the "potential hazard" in a given waste, choosing to label the potentially highly hazardous materials as Priority I Hazardous Wastes, and the potentially moderately hazardous materials as Priority II Hazardous Wastes.

Priority I hazardous wastes include all "elementary" toxic materials, viz., materials which are potentially harmful, regardless of their state of chemical combination. Priority I hazardous wastes also include materials which owe their hazardous properties to their molecular arrangement and which fall in hazard grades 3 or 4 in Table 3.1.2A.

Priority II hazardous wastes owe their hazardous properties to their molecular arrangement and fall in hazard grades 1 or 2 in Table 3.1.2A.

All other process wastes are considered essentially nonhazardous in this study if they fall in the essentially nonhazardous section of Table 3.1.2A.

A list of Priority I inorganic chemicals was made up and used during interviews as a checklist to see whether the plant had any of these materials in its waste (see Table 3.1.3A). As the study proceeded, we found that we had to make some judgments as to whether certain wastes had significant concentrations of "hazardous" metals, as trace quantities of metals can be found in almost any waste. Because of the approximately 15,000 active ingredients used in the pharmaceutical industry, a similar list for organic compounds was impractical. The industry also uses some quantity of practically every organic solvent commercially available, either in its R&D groups or production plants. As will be described later, wastes from these solvents are incinerated. In this preliminary study we were not attempting to catalog all possible components of waste streams, but were merely trying to identify major hazardous wastes. In general, we were looking for information on waste solvents, still bottoms, and solid wastes such as process "muds" or presscakes that were discharged from the plants manufacturing active medicinal ingredients. Representative solvents and still bottoms containing these solvents are characterized in Table 3.1.3B.

## TABLE 3.1.3A

## PRIORITY I HAZARDOUS WASTES

**Inorganic Elements and Compounds**

Mercury
Cadmium } on first proposed toxic pollutant list*
Cyanide
Antimony
Arsenic
Azides
Barium
Beryllium
Chromium (chromates)
Cobalt
Copper
Fluorides
Lead
Molybdenum (molybdates)
Nickel
Nitrites
Osmium
Selenium
Silver
Thallium
Tin
Uranium
Vanadium
Zinc
Radioactive elements

*Published in the Federal Register, 38FR 35388, December 27, 1973.

## TABLE 3.1.3B

## CHARACTERIZATION OF TYPICAL WASTE SOLVENTS OR STILL BOTTOMS CONTAINING THE LISTED CHEMICALS

| Priority I (Highly Hazardous) | Priority II (Moderately Hazardous) |
|---|---|
| Acetone | Ethylene Glycol Monomethyl Ether |
| Acetonitrile | Heptane |
| Amyl Acetate | Methylene Chloride |
| Benzene | Naphtha |
| Butanol | |
| Butyl Acetate | |
| Chloroform* | |
| Ethanol | |
| Ethylene Dichloride | |
| Isopropyl Alcohol | |
| Methanol | |
| Methyl Isobutyl Ketone | |
| Toluene | |
| Xylene | |

*Chloroform would normally be in the Priority II classification, but possible carcinogenic action causes its shift to Priority I.

Anyone considering landfilling of returned pharmaceuticals or disposal of active ingredients is concerned with the possible hazardous properties of the ingredients. Formulated pharmaceuticals and most active medicinal ingredients are not hazardous because of flammability, reactivity with water, self-reactivity, or corrosiveness to skin or eyes. Likewise these products do not usually produce vapors that are toxic on inhalation. The principal hazard categories that would place these pharmaceuticals or ingredients in the hazardous classification are aquatic toxicity ($TL_m$), oral toxicity ($LD_{50}$), bio-concentration or carcinogenicity. It is unlikely that the Food and Drug Administration would leave a pharmaceutical on the market for general use that is a known carcinogen. There are essentially no data on the $TL_m$ values of these compounds and on their bio-concentration in natural flora and fauna. However, there are extensive data on the oral toxicity of these compounds in test animals.

We therefore decided to evaluate the toxicity of the most common products in five of the largest selling pharmaceutical categories: analgesics, antibiotics, ataractics, cardiovasculars, and hormones. The oral $LD_{50}$ values of typical compounds under each pharmaceutical category are listed in Table 3.1.3C. As indicated in the summary at the end of Table 3.1.3C, 48 out of 66 compounds were in toxicity grade 1 ($LD_{50}$ of 500 to 5000 mg/kg – essentially nonhazardous), 17 of the 66 were in grade 2 (50-500 mg/kg – moderately hazardous) and only one compound was in grade 3 (5 to 50 mg/kg – highly hazardous). While the pharmaceutical ingredients sometimes may have a high activity for man when they are injected or ingested, the most active ones are usually dispensed in highly diluted forms so that only a small percentage of active ingredient is present in the dosage form. Although some of the active ingredients can qualify as moderately hazardous, we do not consider the typical mix of returned goods that would actually be disposed of on land to be hazardous. It is highly unlikely that the diluted ingredients would be ingested. Nevertheless, some companies have a few products (such as mercurial ointments) that they screen out of their returned goods to ensure that the discarded material is environmentally acceptable. If a company takes the conservative position that all returned goods and discarded products are considered as moderately hazardous until they are examined, the handling and disposal of these compounds can be done without hazard to personnel or the environment.

## 3.2 WASTE GENERATION DATA DEVELOPMENT

### 3.2.1 Approach to the Problem of Obtaining Valid Industry Hazardous Waste Data

No Federal law has yet been passed requiring industry to obtain and report data on hazardous materials produced as wastes destined for land disposal. To conduct this study it was therefore imperative to obtain the voluntary cooperation of companies that represented a significant portion of the U.S. production of pharmaceutical products. Fortunately, the Pharmaceutical Manufacturers Association (PMA) supported the planned attempt to obtain useful information on which EPA's Office of Solid Wastes Programs could base its future planning and programs. The PMA Environmental Control Committee lent us its support and assisted in obtaining the cooperation of several major pharmaceutical producers.

## TABLE 3.1.3C

## TYPICAL TOXICITIES OF PHARMACEUTICAL ACTIVE INGREDIENTS AS MEASURED BY ORAL LD$_{50}$ ON MICE AND RATS*

| | | Oral LD$_{50}$ (mg/kg) | | |
|---|---|---|---|---|
| **Drug Class** | **Compound** | **Mouse** | **Rat** | **Reference** |
| Analgesics | A | | 2404 | 1 |
| | B | 815 | 1500 | 2,3 |
| | C | | 4025 | 4 |
| | D | | 748 | 4 |
| | E | | 542 | 5 |
| | F | 18 | | 1 |
| | G | | 170 | 6 |
| | H | | 95 | 7 |
| | I | | 887 | 8 |
| | J | 693 | | 9 |
| | K | | 1650 | 10 |
| | L | 84 | | 5 |
| | M | | 1890 | 1 |
| | N | | 1600 | 11 |
| Antibiotics | A | > 3750 | | 12 |
| | B | | 1188 | 1 |
| | C | | 2500 | 13 |
| | D | | 3400 | 1 |
| | E | | 3000 | 12 |
| | F | 2618 | | 14 |
| | G | | 2372 | 1 |
| | H | | 2000 | 15 |
| | I | 4600 | | 16 |
| | J | | 1447 | 1 |
| | K | | > 4000 | 17 |
| | L | > 2880 | | 12 |
| | M | | 4800 | 18 |
| | N | | 300 | 1 |
| | O | 808 | 807 | 1 |
| | P | | 3579 | 1 |
| | Q | | 3550 | 1 |
| | R | | 702 | 1 |

*Table references follows table.

## TABLE 3.1.3C (Continued)

| | | Oral LD$_{50}$ (mg/kg) | | |
|---|---|---|---|---|
| **Drug Class** | **Compound** | **Mouse** | **Rat** | **Reference** |
| Ataractics | A | | 433 | 19 |
| | B | 126 | 548 | 20,1 |
| | C | | 710 | 1 |
| | D | 148-176 | 346-460 | 21 |
| | E | | 840 | 1 |
| | F | >515 | | 22 |
| | G | | 710 | 23 |
| | H | 980 | 1552 | 24,1 |
| | I | | 318 | 19 |
| | J | 150 | | 25 |
| | K | 1250 | 1800 | 4,26 |
| | L | | 995 | 1 |
| | M | 1350 | 740 | 27,26 |
| | N | 330 | | 28 |
| Cardiovasculars | A | | 56 | 1 |
| | B | | 2600 | 1 |
| | C | | 1000 | 29 |
| | D | 213 | | 30 |
| | E | | 2221 | 1 |
| | F | | 1100 | 4 |
| | G | | 1750 | 1 |
| | H | 292 | | 31 |
| | I | | >80 | 32 |
| | J | 300 | 440 | 33,34 |
| | K | 680 | 300 | 35 |
| | L | | 2500 | 26 |
| | M | 890 | | 36 |
| | N | | 1000 | 26 |
| | O | | 3200 | 4 |
| Hormones | A | | >300 | 4 |
| | B | > 2500 | | 37 |
| | C | 1737 | 2952 | 1 |
| | D | 950 | | 1 |

### Oral LD$_{50}$ Summary of Typical Classes of Pharmaceuticals

**(Classified by lower of rat or mouse toxicity values)**

| **Toxicity Grade** | **4 (0-5)** | **3 (5-50)** | **2 (50-500)** | **1 (500-5000)** | **0 (> 5000)** |
|---|---|---|---|---|---|
| Analgesics | 0 | 1 | 3 | 10 | 0 |
| Antibiotics | 0 | 0 | 1 | 18 | 0 |
| Ataractics | 0 | 0 | 6 | 8 | 0 |
| Cardiovasculars | 0 | 0 | 6 | 9 | 0 |
| Hormones | 0 | 0 | 1 | 3 | 0 |
| Total | 0 | 1 | 17 | 48 | 0 |

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37. Klin. Wochenschr., *18,* 156, 1939. (KLWOAZ – Toxic Substance List, 1973)

Because the industry had never had to report detailed composition of waste streams, we realized that mailing of questionnaires would not produce usable information. We therefore chose to conduct in-depth interviews and plant inspections at the plants of the cooperating companies. We visited the principal production plants of companies representing 27 percent of total U.S. sales of ethical pharmaceuticals. These plants represented an even higher percentage of the active ingredient production of the industry. All facilities visited had multiple operations so that good representative information was available on R&D, fermentation, biological products, organic synthesis, extraction of animal glands and formulation and packaging operations in the United States, including Puerto Rico. Information given to us in the interviews and by letter was checked and confirmed with the companies. From the collected data we extrapolated to obtain information applicable to the entire industry.

During the course of the study we also visited eight landfills and four contractors that were treating wastes, principally by incineration. We also interviewed 11 contractors by telephone to confirm information obtained from plant visits.

As explained in Section 2.0 of this report, the SIC codes of the U.S. Department of Commerce do not exactly follow functional divisions of the pharmaceutical industry. For example, we were interested in obtaining information on R&D wastes and the R&D category does not have a SIC code. Another complication in data collection from the plants was that many of the pharmaceutical plants producing active ingredients were diversified, i.e., some parts of the manufacturing complex produced materials for animal feeds, cosmetics, pesticides, fine organic chemicals, etc., as well as medicinal ingredients. For this study we have attempted to isolate those wastes that are associated only with the pharmaceutical production.

The information that we collected on plant visits was categorized under three of the four functional divisions of the pharmaceutical industry: (1) Research and Development, (2) Production of Active Ingredients, and (3) Formulation and Packaging. The fourth functional division, Marketing and Distribution, did not dispose of significant quantities of process wastes or hazardous wastes, as damaged or outdated goods were normally returned to the formulation plants for disposition.

As indicated in Section 2, we considered plants listed as 2831 and 2833 under the production of active ingredients category and plants listed as 2834 under the formulation and packaging category.

#### *3.2.1.1 Wastes from Research and Development Installations*

Based on surveys conducted by the Pharmaceutical Manufacturers Association that show a total of approximately 23,000 personnel employed in research and development (R&D) activities in its member firms, we estimate that total pharmaceutical R&D personnel amount to about 25,000. About one-half of the R&D staff is made up of scientific and professional people and the other half is about equally divided between technical and supporting staff.

R&D activities are often concentrated in research centers run by the industry that employ from 200 to over 2000 R&D personnel so that sizable quantities of wastes may be generated in these centers. On the other hand, some R&D activities are dispersed throughout the individual companies so only a few R&D personnel may be in a given plant, and the R&D wastes may not be segregated.

Depending on the type of research being done the wastes from these activities may involve a heavy use of solvents in one installation while at another installation most of the work may involve tests on animals. Thus in one case there will be waste solvents to be disposed of and in the other there will be test animals to be incinerated. We found that the average mixed solvent waste at the installations we visited was about 66 liters per man-year or a yearly total of approximately 1500 metric tons in the United States.

Other hazardous wastes occurred in much smaller amounts than the solvents and were usually handled as specified by the "Laboratory Waste Disposal Manual" issued by the Manufacturing Chemists' Association. Heavy metal wastes, such as mercury or mercury salts, were often stored until a sufficient quantity was on hand to sell to a reprocessor.

#### *3.2.1.2 Wastes from the Production of Active Ingredients*

In addition to the active ingredients that it produces itself, the pharmaceutical industry purchases many of its active ingredients from chemical companies that are not really in the pharmaceutical industry. Most of the plants listed under SIC 2831 (Biological Products) are a part of the pharmaceutical industry and manufacture active ingredients consumed by the industry. On the other hand, many of the products listed under "Medicinal Chemicals" by the U.S. Tariff Commission are manufactured by chemical companies that are not in the pharmaceutical business. A good example of the latter is choline chloride in the "Medicinal Chemicals" category, which is made almost entirely by chemical companies, but which is used almost entirely in animal feed production. We have subtracted substances such as choline and other materials that are made mostly by the chemical companies to arrive at the active ingredient production that could be assigned to SIC code 2833. We estimate that the pharmaceutical industry's 1973 production of organic medicinal ingredients, excluding antibiotic production, was no more than 34,000 metric tons (75 million pounds).

In the subsections that follow, we discuss methods of active ingredient production and the generation of process and hazardous wastes. We have selected the processes shown from the open literature, and they are typical of industry practice, but do not refer to a specific company's installation.

### 3.2.1.2.1 Synthetic Organic Medicinal Chemicals

The production of organic medicinal chemicals may involve the chemical (or biological) modification of an antibiotic, botanical, or drug from animal sources, or it might be the complete chemical synthesis of a complex chemical, such as vitamin A, whose synthesis starts with acetone, acetic acid, acetylene, and methyl vinyl ketone. Unlike the "heavy chemicals," those chemicals which are produced by the chemical industry in thousands of tons annually, the total annual production of any given organic chemical medicinal might only be 1 or 2 tons. Heavy chemicals are produced in continuous processes and generate a uniform waste stream, but many different medicinals are produced in single batches which causes a wide variation in their waste streams.

The amount of process waste generated per ton of product will vary greatly, depending on the number of synthesis steps, the yield in each step, and the solvents used. The chemical synthesis may only require a two-step synthesis with recovery of unreacted raw materials, such as in aspirin production, or as many as 13 steps as in the production of vitamin A. With an overall yield of over 80%, less than 0.2 kg of organic residue waste would be generated per kg of aspirin, whereas the overall yield in the production of vitamin A might be as low as 15-20%, thus generating as much as 7 kg of organic waste per kg of product. The by-product organic residue waste material is separated from the main product by any of a number of methods such as extraction, distillation, precipitation, crystallization, or filtration, and may be recovered as hard still bottoms, chemical muds, or in a solvent solution. This residue may still contain residual hazardous organics such as hydroquinone, pyridine, or oxalic acid.

Wastewater from the production of organic medicinal chemicals (containing up to several thousand ppm of biodegradable organics such as isopropanol, acetone, ethanol, or acetic acid) must be treated to meet effluent requirements.* This wastewater is usually treated biologically, such as an activated sludge treatment, either on-site or in local municipal treatment systems. This biological treatment, in turn, generates from 0.3 to 0.7 kg of biological sludge solids per kg of organic solids removed, the remainder being converted to carbon dioxide and water by the biological sludge organisms.

The volume of solvent waste generated depends on the degree to which the solvent is contaminated, to what extent solvent recovery is practiced, and the type of reaction and solvent required. Some reactions, such as hydrogenation, may require no solvent at all; some may use ethanol or acetic acid which is diluted and discharged to biological treatment, while still others may use toluene or benzene which must be recovered or incinerated. A "typical" synthetic organic medicinal chemical production process might be summarized as shown in Figure 3.2.1.2.1.

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*State or Federal.

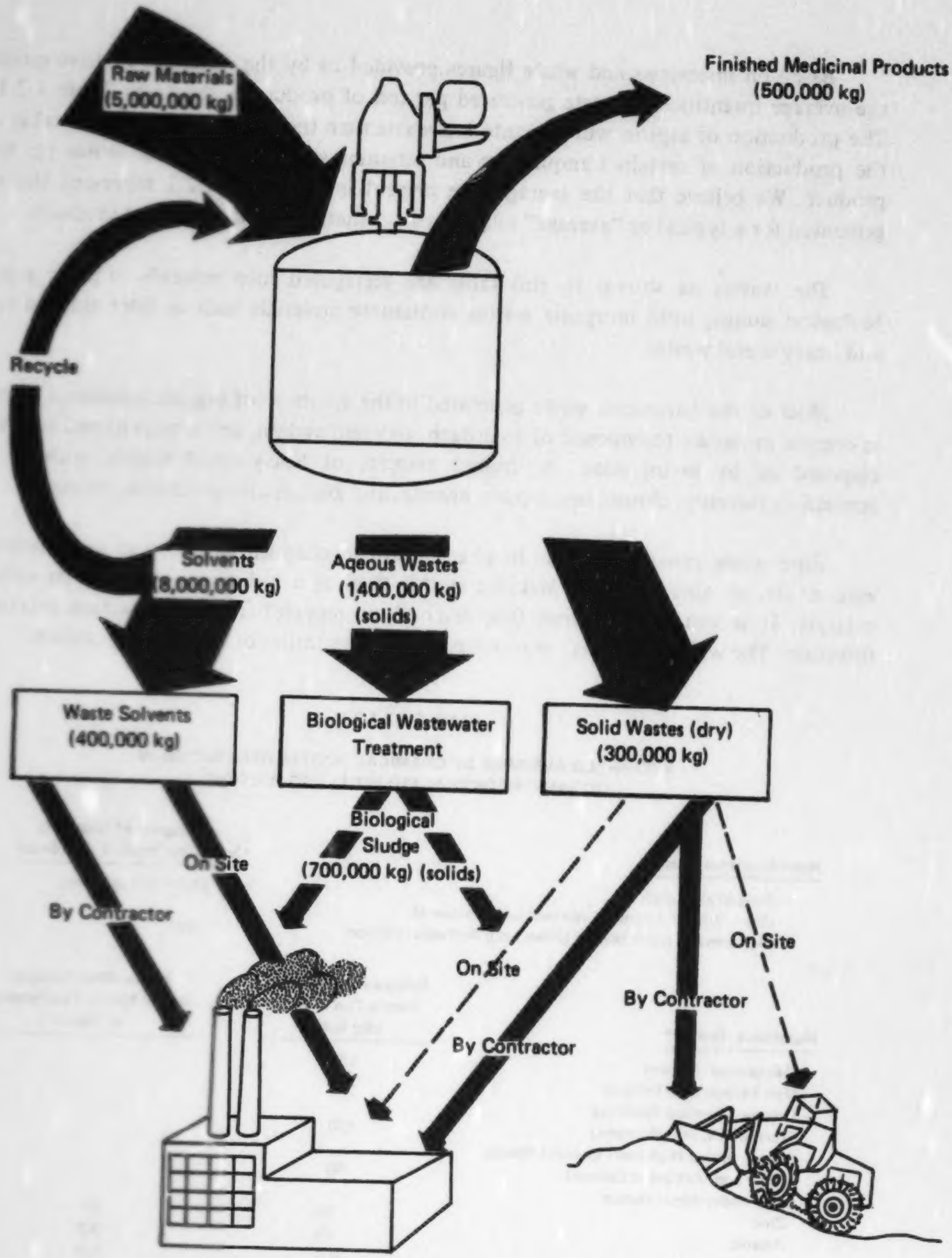
Raw Materials
(5,000,000 kg)
Finished Medicinal Products
(500,000 kg)
Recycle
Solvents
(8,000,000 kg)
Aqeous Wastes
(1,400,000 kg)
(solids)
Waste Solvents
(400,000 kg)
Biological Wastewater
Treatment
Solid Wastes (dry)
(300,000 kg)
Biological
Sludge
(700,000 kg) (solids)
On Site
By Contractor
On Site
On Site
By Contractor
By Contractor
Incineration
Landfill

FIGURE 3.2.1.2.1 TYPICAL SYNTHETIC ORGANIC MEDICINAL CHEMICAL PROCESS

Based on interviews and waste figures provided us by the industry, we have estimated the average quantities of waste generated per ton of product as shown in Table 3.2.1.2.1. The production of aspirin will generate less waste than the averages given in this table while the production of certain tranquilizers and vitamins will generate more waste per ton of product. We believe that the averages we present in Table 3.2.1.2.1 represent the waste generated for a typical or "average" mixture of synthetic organic medicinal products.

The wastes as shown in this table are segregated into solvents, organic residues, biological sludge, solid inorganic wastes containing materials such as filter aid and carbon and heavy metal wastes.

Most of the hazardous waste generated in the synthesis of organic medicinal chemicals is organic in nature (composed of hydrogen, oxygen, carbon, and nitrogen) and is generally disposed of by incineration. A limited amount of heavy-metal wastes, such as those containing mercury, chromium, copper, arsenic, and zinc, is also generated, however.

Zinc waste generally occurs in pharmaceutical chemical production as metallic zinc, zinc oxide, or zinc chloride. Metallic zinc is used as a reducing agent and its salts as a catalyst. It is usually recovered (for disposal or recycle) from the reaction mixture by filtration. The waste zinc salts are recovered by precipitation or solvent evaporation.

### TABLE 3.2.1.2.1

### ESTIMATED AVERAGE OF CHEMICAL WASTES GENERATED IN ORGANIC MEDICINAL CHEMICAL PRODUCTION†

| Non-Hazardous Waste | Kilogram of Waste per Metric Ton Product (dry basis) |
|---|---|
| – Biological Sludge (from Organic Chemical Wastewater Treatment) | 1400* (14,000 wet) |
| – High Inert Content Wastes (Filter and, Activated Carbon) | 100 |

| Hazardous Wastes** | Kilogram of Waste per Metric Ton Product (dry basis) | Heavy Metal Content (kg Per Metric Ton Product of Waste) |
|---|---|---|
| – Halogenated Solvent | 100 | |
| – Non Halogenated Solvent | 700 | |
| – Organic Chemical Residues (Tars, Muds, Still Bottoms) | 400 | |
| – Contaminated High Inert Content Wastes (Filter and, Activated Carbon) | 50 | |
| – Solid Heavy-Metal Wastes | | |
| Zinc | 70 | 30 |
| Arsenic | 15 | 0.3 |
| Chromium | 0.7 | 0.3 |
| Copper | 0.1 | 0.04 |
| Mercury | 0.02 | 0.01 |

*From 2800 kg of solids in organic chemical wastewater.

**Contains some heavy metal, corrosive chemical, or flammable solvent

†Source: Interviews and A.D. Little, Inc., estimates.

To put the 2,200 metric tons/yr of zinc waste landfilled by the pharmaceutical industry in perspective, an estimated 36,000 metric tons of zinc oxide annually finds its way into landfills throughout the United States as photocopy paper.

Arsenic wastes are generated in the pharmaceutical industry as a by-product of arsenical production and where arsenic compounds are used as catalysts or oxidizing agents.

We do not believe there is widespread use of chromium or chromium salts in the pharmaceutical industry. The oxide is used in the heavy chemical industry as one of many catalysts for hydrogenation and oxidation, and as an oxidizing agent in some organic chemical syntheses. However, many of these oxidation (dehydration) reactions can be conducted, using other oxidizing agents, such as chlorates, peroxides or permanganates. In the one case where we know that chromium is being used in the pharmaceutical industry, the chromium waste is recovered by precipitation and filtration and then sold.

We know of only one pharmaceutical company which produces a copper waste, and it is presently disposed of by deep-well injection.

We estimate that organic mercury wastes containing about 270 kg of elemental mercury are produced by the pharmaceutical industry annually. A limited number of pharmaceutical companies produce the mercurial products which include nitromersol and thimerosal. These companies take considerable care to ensure that mercury is removed from the plant wastewater effluents.

There are a number of processes available for the removal of mercury from wastewater. Ion exchange, solvent extraction, carbon adsorption, sulfide precipitation, cementation, and reduction/precipitation have all been used with varying degrees of success. The type of mercury-removal process that should be used for a specific application depends on the following:

- Concentration of mercury in the wastewater;
- Maximum allowable concentration of mercury in effluent;
- Chemical form of the mercury to be removed;
- Type and quantity of other chemical constituents in the wastewater; and
- Desirability of recovering metallic mercury.

According to our investigations, reduction/precipitation processes are being used increasingly where the wastewater flow rate is relatively small and intermittent. Mercury is recovered either as pure metallic mercury or as an amalgam.

In the most common reduction/precipitation process, which is currently being commercialized, a caustic solution of sodium borohydride ($NaBH_4$) is mixed with the mercury-containing wastewater where the ionic mercury is directly reduced to metallic mercury which rapidly precipitates out of solution. The following reaction occurs:

$$4\,Hg^{2+} + BH_4^- + 8\,OH^- = 4\,Hg + B(OH)_4^- + 4\,H_2O$$

If the mercury solution is in the form of an organic complex, the driving force of the reduction reaction may not be sufficient to break the complex. In that case, the wastewater must be chlorinated prior to the reduction step to break down the metal-organic bond.

When elemental mercury recovery is not desired, the reduction process can be used to form mercury amalgams to produce a less hazardous solid waste for ultimate disposal by encapsulation and landfill.

#### 3.2.1.2.2 Inorganic Medicinal Chemicals

Antacids make up a major share of inorganic medicinal chemical production. Generally antacids have magnesium hydroxide or aluminum hydroxide as their primary active ingredient. These antacids are produced by precipitating a water-insoluble compound from a solution of a soluble aluminum or magnesium salt by a sodium salt. Some formulations also include magnesium trisilicate, calcium carbonate, sodium bicarbonate, alumina gel, and bismuth aluminate. The waste stream generated contains no toxic metals or salts and is usually a solution of sodium chloride or sodium sulfate. Bad batches of antacid active ingredient may occasionally be produced, and these are either reprocessed or disposed of by landfilling, but they would also be considered nonhazardous.

We did find one toxic metal-containing waste generated in the production of inorganic medicinal chemicals. This waste contains about 0.2% selenium and amounts to about 160,000 kg annually.

The pharmaceutical industry produces several laxatives of botanical origin such as senna, cascara, and a synthetic organic medicinal, phenolphthalein. However, milk of magnesia (magnesium hydroxide suspension) is the principal inorganic laxative. The production of magnesium hydroxide for this use would also generate aqueous sodium sulfate or sodium chloride.

Active ingredients for many other inorganic medicinals are purchased for products such as mouthwashes, throat lozenges, and topical medicinals, such as the mercurials, zinc oxide ointments, and foot powders. Since these purchased active ingredients are produced by the chemical industry (rather than the pharmaceutical industry), the only waste containing these purchased ingredients is that generated in the compounding and packaging of pharmaceutical preparations.

### 3.2.1.2.3 Fermentation Products (Antibiotics)

Most commercial antibiotics are the products of living microorganisms, such as fungi (molds) or bacteria. The crude antibiotic produced by the microorganism is recovered from the fermentor broth (a water solution containing nutrients) by extraction, precipitation, or adsorption, depending on the type of antibiotic. Bacitracin, the penicillins, cephalosporins, and erythromycins are usually recovered from the filtered broth by solvent extraction. Chlortetracycline is recovered by solvent extraction of the whole broth (containing mycelium) or filtered broth. Streptomycin is recovered from the filtered broth by ion exchange. Oxytetracycline is recovered from the filtered broth by precipitation with a quaternary ammonium compound.

Following recovery from the fermentor broth, the antibiotic is purified, in most cases, by several stages of recrystallization. Other antibiotics, such as the semi-synthetic penicillins and cephalosporin derivatives, are produced by chemically modifying antibiotics produced by fermentation.

The production of antibiotics results in the generation of several large waste streams: the filtered micro-organism (mycelium*); the filtered, extracted, fermentor broth; and contaminated solvent generated in the solvent recovery operation.

The fermentor broth is sometimes concentrated and sold as an animal feed supplement, but in most cases the fermentor broth and other wastewater streams are treated biologically to meet effluent requirements. The 0.3 to 0.7 kg of biological sludge generated per kg of dissolved organics removed in wastewater treatment is either landfilled or incinerated.

A good example of antibiotic production (and a large volume product) is penicillin as shown in Table 3.2.1.2.3 and Figure 3.2.1.2.3.

Commercial penicillin is produced by the submerged-culture fermentation process in which a strain of *Penicillium* mold is grown in an aerated, stirred tank, the fermentor, in a water medium. This medium contains carbohydrates (starches, sugars) as an energy source, nitrogen in the form of ammonium salts or corn-steep liquor solids for mycelium cell wall protein, and trace minerals, such as magnesium, which are necessary for growth. Rapid growth of the mycelium takes place during the first 24 to 48 hours and the production of penicillin takes place from 24 to 120 hours.

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*The term mycelium should be reserved for describing the thread-like growth of molds, such as Penicillium, or the analagous growth in Actinomyces. However, the term is commonly used in the industry to designate the mixture of cells, filter aid, undigested grain solids, etc., that is filtered off and discarded from all types of fermentations, including bacterial fermentations that do not produce true mycelia.

## TABLE 3.2.1.2.3

## TYPICAL ANTIBIOTIC PRODUCTION PLANT (PROCAINE PENICILLIN G)

A. Annual Production 950,000 kg

B. Waste Characterization

| Non-Hazardous Waste | Stream No. | Weight per 1000 kg Product | |
|---|---|---|---|
| | | Dry | Wet |
| Mycelium | ① | 2,300 kg | 10,000 kg |
| Biological sludge | ⑨ | 3,500 kg | 35,000 kg |

| Non-Hazardous Waste to Biological Treatment | Stream No. | Liters per 1000 kg Product |
|---|---|---|
| Waste fermentation broth | ③ | 56,000 |
| Crystallization water | ④ | 100 |
| Phosphate buffer solution | ⑤ | 3,000 |
| Crystallization water | ⑦ | 100 |
| Potassium chloride solution | ⑧ | 4,000 |

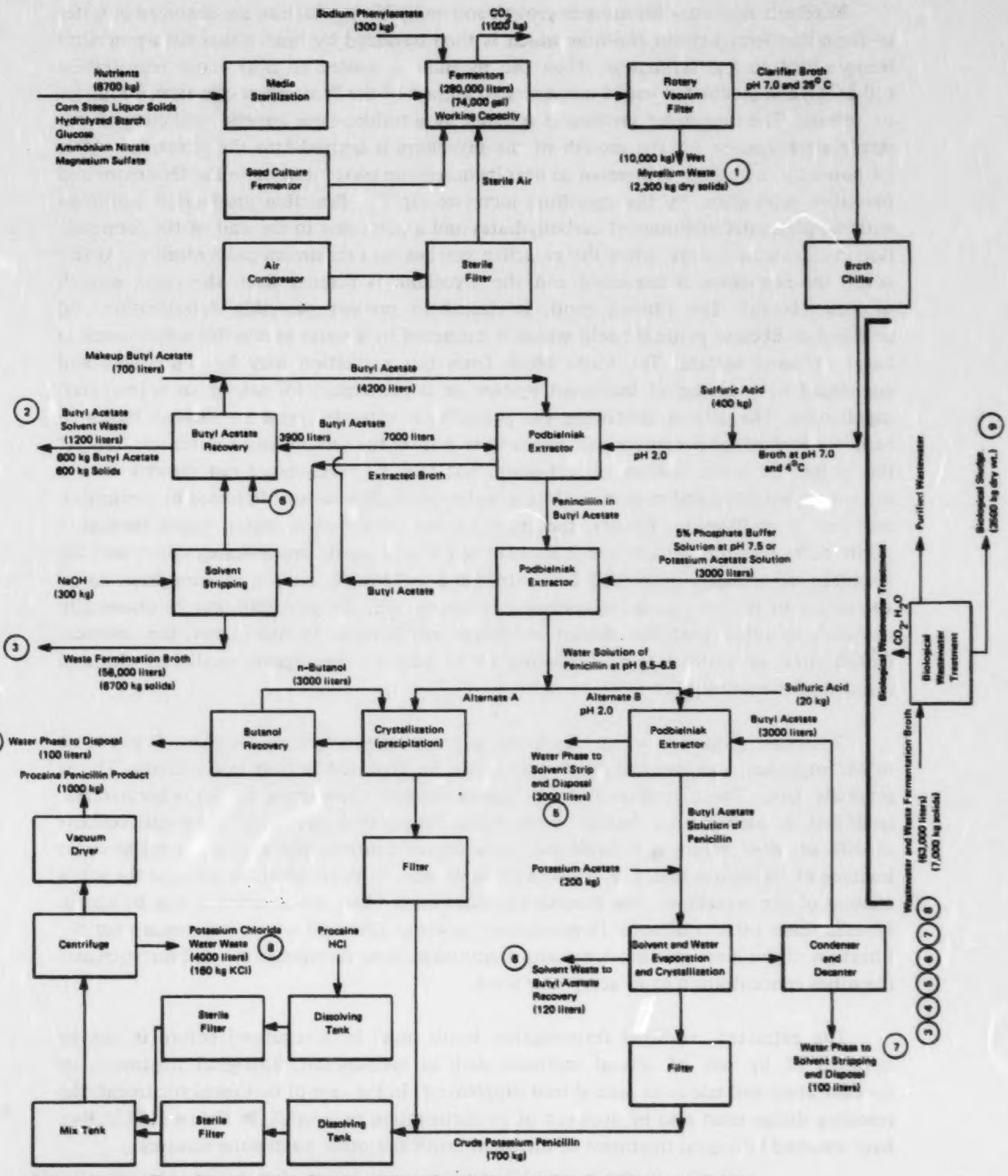
| Hazardous Waste | Stream No. | Liters per 1000 kg Product |
|---|---|---|
| Solvent Waste Concentrate | ② | 1,200 |
| Solvent (butyl acetate) | | 600 |
| Dissolved organics (fats, protein) | | 600 |

**Source:** Arthur D. Little, Inc., estimates.

Carbohydrate is fed to the fermentor over the course of the fermentation as an energy source for the mycelium. After the initial mycelium growth phase, a precursor, such as phenylacetic acid or its salts, is added to increase production of a specific type of penicillin. The mold uses this precursor directly in producing the penicillin. With phenylacetic acid, the yield of penicillin G is greatly increased.

The strain of penicillium, the exact composition of the growth medium, the yield of penicillin, and some details of the purification of the penicillin are trade secrets of the manufacturers. The penicillin produced and recovered from the fermentation may also be chemically modified to produce one of many commercial penicillins, but the fermentation process for initially producing the basic penicillin is generally the same.

A typical penicillin production process (Figure 3.2.1.2.3) consists of the initial fermentation in which the antibiotic is produced by the micro-organism, the recovery of the crude antibiotic from the fermentation broth by several stages of solvent and aqueous buffer extraction, crystallization of the crude antibiotic, and finally the sterilization of the antibiotic. The same process steps are used by many producers, but the exact conditions of pH and temperature and extraction procedures (type of extractor, type of solvent, etc.) will vary from producer to producer. Likewise there was some variation in quantity of mycelium waste reported by our industrial contacts. Nonetheless we believe that the system for penicillin production, as shown in Figure 3.2.1.2.3, is representative of industry practice and is representative of the types and quantities of waste generated in penicillin production and antibiotic production in general.


Sodium Phenylacetate (300 kg)
CO2 (1000 kg)
Nutrients (8700 kg)
Corn Steep Liquor Solids
Hydrolyzed Starch
Glucose
Ammonium Nitrate
Magnesium Sulfate
Media Sterilization
Fermentors (280,000 liters) (74,000 gal) Working Capacity
Rotary Vacuum Filter
Clarifier Broth pH 7.0 and 25° C
Seed Culture Fermentor
Sterile Air
(10,000 kg) Wet Mycelium Waste (2,300 kg dry solids)
1
Air Compressor
Sterile Filter
Broth Chiller
Makeup Butyl Acetate (700 liters)
Butyl Acetate (4200 liters)
2
Butyl Acetate Solvent Waste (1200 liters)
600 kg Butyl Acetate
600 kg Solids
Butyl Acetate Recovery
Butyl Acetate
3900 liters
7000 liters
Podbielniak Extractor
Sulfuric Acid (400 kg)
pH 2.0
Broth at pH 7.0 and 4°C
Extracted Broth
6
Penincillin in Butyl Acetate
5% Phosphate Buffer Solution at pH 7.5 or Potassium Acetate Solution (3000 liters)
NaOH (300 kg)
Solvent Stripping
Butyl Acetate
Podbielniak Extractor
3
Waste Fermentation Broth (56,000 liters) (8700 kg solids)
Water Solution of Penicillin at pH 6.5–6.8
n-Butanol (3000 liters)
Alternate A
Alternate B
pH 2.0
Sulfuric Acid (20 kg)
Butyl Acetate (3000 liters)
4
Water Phase to Disposal (100 liters)
Butanol Recovery
Crystallization (precipitation)
Podbielniak Extractor
Water Phase to Solvent Strip and Disposal (3000 liters)
5
Procaine Penicillin Product (1000 kg)
Vacuum Dryer
Filter
Butyl Acetate Solution of Penicillin
Potassium Acetate (200 kg)
Centrifuge
Potassium Chloride Water Waste (4000 liters) (160 kg KCl)
8
Procaine HCl
6
Solvent Waste to Butyl Acetate Recovery (120 liters)
Solvent and Water Evaporation and Crystallization
Condenser and Decanter
Sterile Filter
Dissolving Tank
Filter
7
Water Phase to Solvent Stripping and Disposal (100 liters)
Mix Tank
Sterile Filter
Dissolving Tank
Crude Potassium Penicillin (700 kg)
Biological Wastewater Treatment
CO2, H2O
Biological Wastewater Treatment
Purified Wastewater
Biological Sludge (3500 kg dry wt.)
9
Wastewater and Waste Fermentation Broth (63,000 liters) (7,000 kg solids)
3
4
5
6
7
8

**Sources:** Brunner, Elder, Prescott, Rehm, Standen, Underkofler, Webb and Arthur D. Little, Inc., estimates (see Bibliography at end of Section).

FIGURE 3.2.1.2.3 REPRESENTATIVE PROCESS FOR ANTIBIOTIC PRODUCTION (PROCAINE PENICILLIN G)

Nutrients necessary for mycelia growth and penicillin production are dissolved in water to form the fermentation medium which is then sterilized by heat, either before or after being added to the fermentor. Then the medium is cooled to near room temperature (20-24°C) and inoculated with a concentrated culture of the Penicillium organism, about 5% by volume. The inoculated medium is agitated by a turbine-type impeller and compressed, sterile air necessary for the growth of the mycelium is sparged into the fermentor. After 24 hours the mycelium has grown to near its maximum concentration in the fermentor and penicillin production by the mycelium increases rapidly. Penicillin production continues with supplemental additions of carbohydrates and a precursor to the end of the fermentation cycle, about 5 days, when the penicillin reaches near maximum concentration. At this point the fermentor is harvested and the mycelium is filtered from the spent growth medium (broth). The filtered broth is chilled to prevent penicillin deterioration and acidified to liberate penicillic acid which is extracted by a water-immiscible solvent such as butyl or amyl acetate. The waste broth from this extraction may be neutralized and discharged to a biological treatment system or concentrated for sale as an animal feed supplement. The solvent containing the penicillin is extracted with an alkaline buffer to form the sodium or potassium salt and remove it from the solvent into a water solution. At this point the crude sodium or potassium salt may be precipitated out directly with a solvent, or acidified and re-extracted by a water-immiscible solvent followed by neutralization and crystallization. Finally, the crude salt is redissolved in water passed through a sterile filter to a mix tank where it is combined with a sterile precipitating agent, and the insoluble sterile salt is recovered by centrifuging and then dried in a vacuum drier. As an alternative to recovery as the potassium or procaine salt, the penicillin may be chemically modified to other penicillin derivatives before sterilization. In this report, the chemical modification of antibiotics is considered to be part of the organic medicinal chemical segment of the industry.

Since the medium in which this living organism, the mycelium, is grown is not toxic to the organism, the spent medium would also be expected to have low toxicity. This is generally true. The mycelium from the spent medium (fermentor broth) is incinerated, landfilled, or used as a soil builder. Some states require that mycelium have a solid content of 30% or more before it is landfilled, since higher concentrations of water might cause leaching of hazardous materials from other substances in the landfill. To increase the solids content of the mycelium from penicillin production, a filler such as sawdust may be added. Mycelia from other antibiotic fermentations contains filter aid which is necessary for the filtration of the more gelatinous mycelia produced in these fermentations, and this increases the solids concentration to an acceptable level.

The extracted, acidified fermentation broth must be neutralized before it can be disposed of by one of several methods such as incineration, biological treatment, or concentration and sale as an animal feed supplement. In the case of biological treatment, the resulting sludge must also be disposed of by incineration or landfill. In figure 3.2.1.2.3 we have assumed biological treatment of the spent broth and other wastewater streams.

The only hazardous wastes resulting from antibiotic production are the waste solvents which contain organic material from the extracted broth and which are generated in the recovery of the major portion of the solvent used in the process. In this report, any chemical wastes from antibiotic modification are considered to be part of synthetic organic medicinal chemical production.

### 3.2.1.2.4 Botanicals

The pharmaceuticals produced from plant material – leaves, bark, and roots – include the alkaloids such as quinine and reserpine, plant steroids for chemical synthesis of cortisones and oral contraceptives, and laxatives such as emodin from cascara bark.

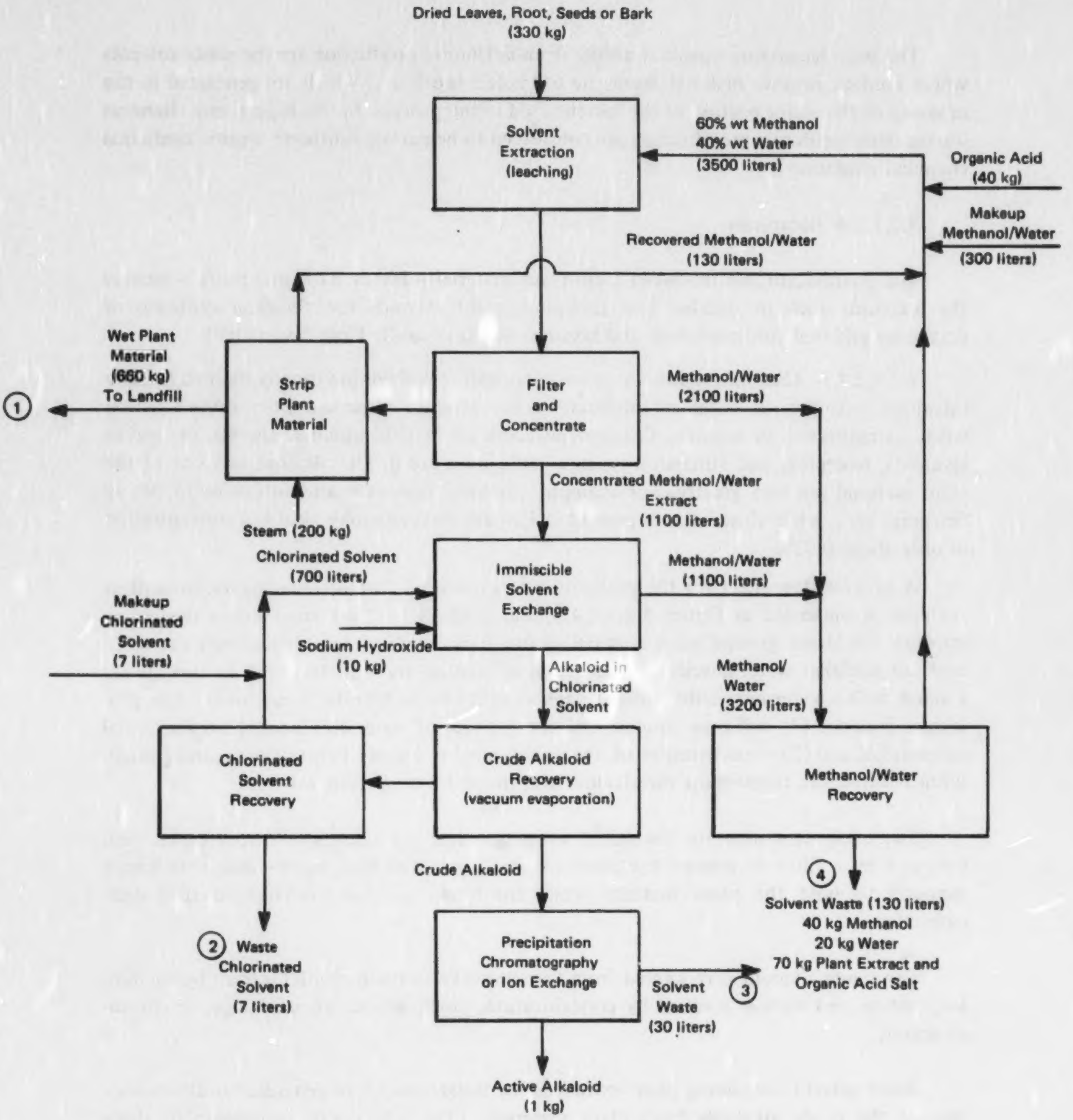
*3.2.1.2.4.1 Alkaloid Production from Botanicals* Alkaloids are usually defined as basic (alkaline), nitrogenous botanical products which produce a marked physiological action when administered to animals. Commercial alkaloids include quinine, emodin (a cascara alkaloid), reserpine, and vincristine (a new anticancer drug). The alkaloid content of the plant material can vary greatly. For example, quinine is present in amounts of up to 10% in cinchona bark, while vinscristine is present in *Vinca rosea* (periwinkle) leaf in a concentration of only about 0.02%.

A process flow sheet for the production of a (alkaloid) botanical medicinal from plant material is presented as Figure 3.2.1.2.4.1, and Table 3.2.1.2.4.1 summarizes the wastestreams. The dried, ground plant material (roots, bark, seeds, or leaf) is generally extracted with an acidified water-miscible solvent such as alcohol and this leachate, in turn, is extracted with a water-immiscible solvent such as ethylene dichloride. Variations in this procedure include: (1) using an aqueous solvent mixture of water and alcohol for the initial extractions, and (2) concentration of the initial alcohol extract before the second (liquid-liquid) extraction, transferring the alkaloid into the water-immiscible solvent.

The equipment used for the initial extraction may be a series of stirred tanks, each followed by a filter to remove the plant material, or a series of vessels with wire screen supports to hold the plant material while the leaching solvent is changed after each extraction.

The crude alkaloid is recovered from the second (water-immiscible) solvent by vacuum evaporation and further purified by crystallization, precipitation, ion exchange, or chromatography.

Waste solvent containing plant extract is the hazardous waste generated in the extraction of the crude alkaloids from plant materials. (The subsequent conversion of these alkaloids to other derivatives may create additional hazardous wastes, but these wastes would be included in organic medicinal chemical production.) The extracted plant material waste must be steamed, however, to remove residual solvent that would otherwise pose a fire hazard.


Dried Leaves, Root, Seeds or Bark
(330 kg)
Solvent
Extraction
(leaching)
60% wt Methanol
40% wt Water
(3500 liters)
Organic Acid
(40 kg)
Makeup
Methanol/Water
(300 liters)
Recovered Methanol/Water
(130 liters)
Wet Plant
Material
(660 kg)
To Landfill
①
Strip
Plant
Material
Filter
and
Concentrate
Methanol/Water
(2100 liters)
Concentrated Methanol/Water
Extract
(1100 liters)
Steam (200 kg)
Chlorinated Solvent
(700 liters)
Immiscible
Solvent
Exchange
Methanol/Water
(1100 liters)
Makeup
Chlorinated
Solvent
(7 liters)
Sodium Hydroxide
(10 kg)
Alkaloid in
Chlorinated
Solvent
Methanol/
Water
(3200 liters)
Chlorinated
Solvent
Recovery
Crude Alkaloid
Recovery
(vacuum evaporation)
Methanol/Water
Recovery
Crude Alkaloid
④
Solvent Waste (130 liters)
40 kg Methanol
20 kg Water
70 kg Plant Extract and
Organic Acid Salt
② Waste
Chlorinated
Solvent
(7 liters)
Precipitation
Chromatography
or Ion Exchange
Solvent
Waste
(30 liters)
③
Active Alkaloid
(1 kg)

**Source:** Forbath, Manske, Nobler and Arthur D. Little, Inc., estimates. (See Bibliography)

FIGURE 3.2.1.2.4.1 REPRESENTATIVE PROCESS FOR BOTANICAL MEDICINALS (PLANT ALKALOIDS)

## TABLE 3.2.1.2.4.1

## TYPICAL PLANT FOR PRODUCING BOTANICAL MEDICINALS (PLANT ALKALOIDS)

A. Annual Production 680 kg

B. Waste Characterization

| | Stream No. | Weight per kg Product | |
|---|---|---|---|
| | | Dry | Wet |
| Non-Hazardous Waste | | | |
| Wet botanical material | ① | 330 kg | 660 kg |

| | Stream No. | kg per kg Botanical Material | Quantity per kg Product | |
|---|---|---|---|---|
| | | | Liters | kg |
| Hazardous Waste | | | | |
| Halogenated solvent | ② | 0.03 | 7 | 9 |
| Methanol — water concentrate | ④ | 0.36 | 130 | 120 |
| Non-halogenated solvent | ③ | 0.06 | 30 | 20 |

Source: Arthur D. Little, Inc., estimates.

The solvent waste generated in the initial extraction will contain alcohol, water, and dissolved plant extract (resins, fats, etc.). In the second step of alkaloid isolation, extraction of the alkaloid from the aqueous leaching solvent into a water-immiscible solvent, much of the water-soluble organic material is left behind in the aqueous solvent. Consequently, not as much of this second solvent (e.g., chlorinated solvent) becomes waste in this process.

In the final purification steps (e.g., crystallization, precipitation) of the alkaloid, additional waste solvent is generated.

*3.2.1.2.4.2 Steroid Production from Botanicals* Most of the steroid products now produced commercially were originally extracted from animal organs, requiring tons of animal organs to produce a few grams of hormone. When the structures of the various hormones and other steroids were determined and synthesis routes were developed, it became possible to produce many of these hormones commercially on a large scale from steroids present in plant materials. Soybeans and Mexican yams now supply the steroids stigmasterol and diosgenin, respectively, used in the commercial production of cortisone derivatives and oral contraceptives.

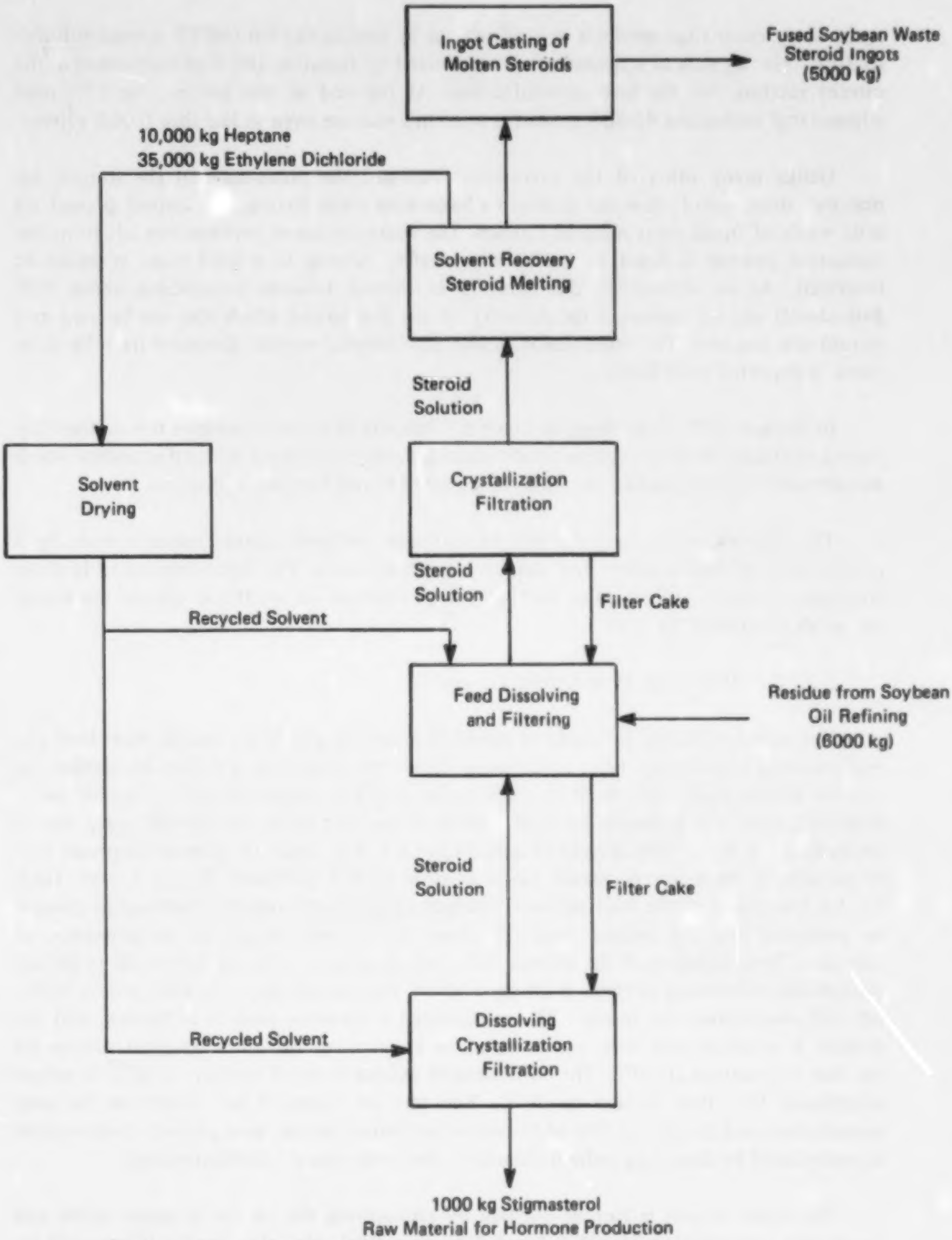
In 1964, over 70% of the cortical hormones were produced from diosgenin from Mexican yams. Since a high export tax must be paid in Mexico on shipments of crude product, the diosgenin is extracted from the yams and purified or converted to other steroid derivatives before export to the United States. Stigmasterol is produced in the United States by the solvent extraction of soybean oil distillation residue. Table 3.2.1.2.4.2 summarizes the wastestreams and Figure 3.2.1.2.4.2 shows a representative flow diagram for the latter process.

**TABLE 3.2.1.2.4.2**

**TYPICAL PLANT FOR PRODUCING BOTANICAL MEDICINALS**
**(STIGMASTEROL FOR HORMONE SYNTHESIS)**

| | |
|---|---|
| A. Annual Production of Stigmasterol | 130 Metric Tons |
| B. Waste Characterization | **Weight per MT Product** |
| Non-Hazardous Waste | |
| Fused Soybean Steroid Ingots | 5000 kg |

Still bottoms from soybean oil refining, which contain around 20% stigmasterol and about 45% β-sitosterol, are dissolved in a hot solvent mixture of hexane and ethylene dichloride. About 1000 kg of 97% stigmasterol product and 5000 kg of residue are generated from 6000 kg of feed steriods through a series of crystallizations from a solvent mixture of 63% ethylene dichloride and 37% hexane by volume. In each crystallization step,


Ingot Casting of Molten Steroids
Fused Soybean Waste Steroid Ingots (5000 kg)
10,000 kg Heptane
35,000 kg Ethylene Dichloride
Solvent Recovery Steroid Melting
Steroid Solution
Solvent Drying
Crystallization Filtration
Steroid Solution
Filter Cake
Recycled Solvent
Feed Dissolving and Filtering
Residue from Soybean Oil Refining (6000 kg)
Steroid Solution
Filter Cake
Recycled Solvent
Dissolving Crystallization Filtration
1000 kg Stigmasterol Raw Material for Hormone Production

**Sources:** Poulos et al and Arthur D. Little, Inc., estimates. (See Bibliography)

FIGURE 3.2.1.2.4.2 REPRESENTATIVE PROCESS FOR BOTANICAL MEDICINALS (STIGMASTEROL FOR HORMONE SYNTHESIS)

successively purer stigmasterol is crystallized out by cooling the hot (60°C) solvent solution to 30°C. The crystals of stigmasterol are recovered by filtration and then redissolved in the solvent mixture for the next crystallization. At the end of the process, the 97% pure stigmasterol containing 45-50% solvent is dried in a vacuum oven to less than 0.06% solvent.

Unlike many other of the extraction processes, the production of the steroid raw material, stigmasterol, does not generate a hazardous waste stream, but instead generates a solid waste of fused plant material steroids. The waste residue of soybean steroids from this extraction process is fused at 160°C which, after cooling to a solid mass, is stored or landfilled. As an alternative, this mixture of steroid residues (containing about 50% β-sitosterol) can be processed for recovery of the β-sitosterol which also can be used as a steroid raw material. The other major steroid raw material source, diosgenin from Mexican yams, is imported from Mexico.

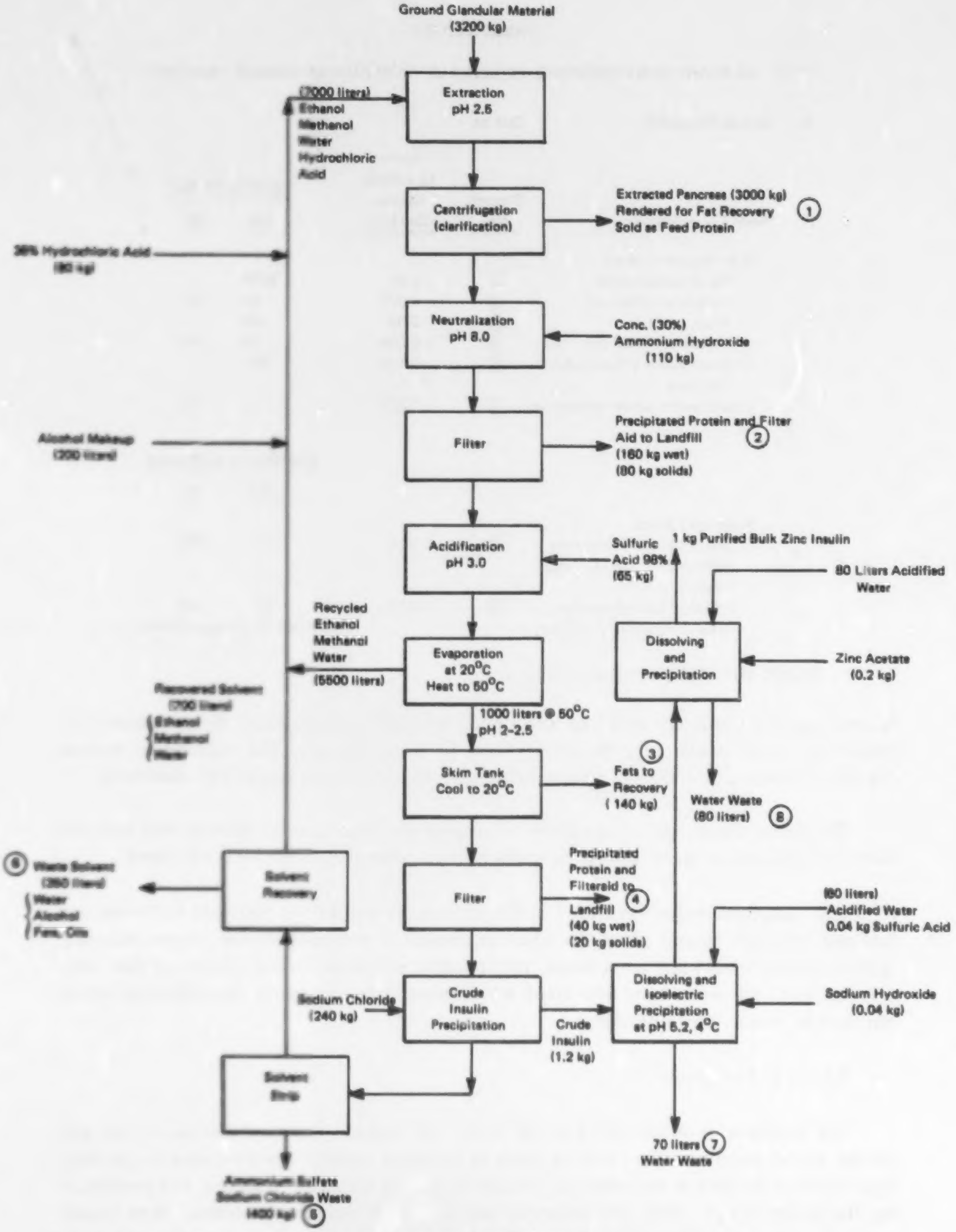
In January 1975, G.D. Searle & Company announced plans to produce raw material for steroid synthesis by fermentation of the steroid, β-sitosterol. Some of the β-sitosterol which was formerly a waste product may thus be recycled to produce other products.

The conversion of these steroids to cortisone and oral contraceptives is done by a combination of fermentation and chemical synthesis steps. The wastes generated in these conversion steps is included as part of the production of synthetic organic medicinal chemicals (Section 3.2.1.2.1).

### 3.2.1.2.5 Medicinals from Animal Glands

The major medicinal products obtained from animal glands are insulin from beef and hog pancreas and heparin from lung tissues. Since the extraction processes are similar, we will use insulin production as an example. On a small scale in the laboratory, insulin can be extracted from the pancreas by acidic water alone, but on a commercial scale this is impractical, so acidic 90% denatured alcohol is used. A process for commercial production of medicinals from animal glands (insulin) is presented in Figure 3.2.1.2.5, and Table 3.2.1.2.5 summarizes the wastestreams. The ground glands are extracted with acidic ethanol or methanol and the extract recovered from the ground glands by centrifugation or filtration. Neutralization of the extract with concentrated ammonium hydroxide to pH 8.0 precipitates extraneous protein. A stronger alkali, such as sodium hydroxide, or too high a pH will decompose the insulin. The precipitated extraneous protein is filtered, and the extract is acidified and then concentrated to about a seventh of its original volume by vacuum evaporation at 20°C. The concentrated extract is raised quickly to 50°C to release solubilized fats, then cooled to 20°C. The fats are skimmed and recovered for soap manufacture and the extract filtered to remove additional precipitated protein. Crude insulin is precipitated by dissolving sodium chloride in the concentrated clarified extract.

The crude insulin is further purified by redissolving the insulin in acidic water and iso-electric precipitation at pH 5.2 and 4°C. In a final step, zinc insulin is prepared by


Ground Glandular Material
(3200 kg)
Extraction
pH 2.5
(2000 liters)
Ethanol
Methanol
Water
Hydrochloric
Acid
Centrifugation
(clarification)
Extracted Pancreas (3000 kg)
Rendered for Fat Recovery
Sold as Feed Protein
①
36% Hydrochloric Acid
(80 kg)
Neutralization
pH 8.0
Conc. (30%)
Ammonium Hydroxide
(110 kg)
Filter
Precipitated Protein and Filter
Aid to Landfill
(160 kg wet)
(80 kg solids)
②
Alcohol Makeup
(200 liters)
Acidification
pH 3.0
Sulfuric
Acid 98%
(65 kg)
1 kg Purified Bulk Zinc Insulin
80 Liters Acidified
Water
Recycled
Ethanol
Methanol
Water
(5500 liters)
Evaporation
at 20°C
Heat to 50°C
Dissolving
and
Precipitation
Zinc Acetate
(0.2 kg)
Recovered Solvent
(700 liters)
Ethanol
Methanol
Water
1000 liters @ 50°C
pH 2-2.5
③
Skim Tank
Cool to 20°C
Fats to
Recovery
(140 kg)
Water Waste
(80 liters)
⑥
⑥
Waste Solvent
(350 liters)
Water
Alcohol
Fats, Oils
Solvent
Recovery
Filter
Precipitated
Protein and
Filteraid to
Landfill
(40 kg wet)
(20 kg solids)
④
(80 liters)
Acidified Water
0.04 kg Sulfuric Acid
Sodium Chloride
(240 kg)
Crude
Insulin
Precipitation
Crude
Insulin
(1.2 kg)
Dissolving and
Isoelectric
Precipitation
at pH 5.2, 4°C
Sodium Hydroxide
(0.04 kg)
Solvent
Strip
70 liters ⑦
Water Waste
Ammonium Sulfate
Sodium Chloride Waste
(400 kg) ⑤

Sources: Standen, Webb, and Arthur D. Little, Inc., estimates. (See Bibliography)

**FIGURE 3.2.1.2.5 REPRESENTATIVE PROCESS FOR MEDICINALS FROM ANIMAL GLANDS (INSULIN – 1 KG OF PRODUCT)**

**TABLE 3.2.1.2.5**

**TYPICAL PLANT FOR PRODUCING MEDICINALS FROM ANIMAL GLANDS (INSULIN)**

| | | | kg per kg Product | |
|---|---|---|---|---|
| **A. Annual Production** | 284 kg | | | |
| **B. Waste Characterization** | **Stream No.** | **kg per kg Animal Glands (Dry Wt.)** | **Dry** | **Wet** |
| Non-Hazardous Waste | | | | |
| Rendered pancreas | ① | 0.94 | 3000 | – |
| Protein and filter aid | ② | 0.025 | 80 | 160 |
| Recovered fats | ③ | 0.04 | 140 | – |
| Protein and filter aid | ④ | 0.006 | 20 | 40 |
| Ammonium sulfate/sodium chloride | ⑤ | 0.125 | 400 | |
| Insulin precipitation wastewater | ⑦ | 0.022 | – | 70 |
| | | | **Quantity per kg Product** | |
| | | | **Liters** | **kg** |
| Hazardous Waste | | | | |
| Waste solvent concentrate (Ethanol, methanol, water, fats, oils) | ⑥ | 0.10 | 350 | 320 |
| Precipitation wastewater (May contain traces of zinc) | ⑧ | 0.025 | 80<br>(1-5 gm Zn per kg product) | 80 |

**Source:** Arthur D. Little, Inc., estimates.

redissolving the insulin in acidified water and then adding zinc acetate to precipitate zinc insulin, or plain insulin may be precipitated by using acetone. The solution of sodium chloride in water and alcohol is solvent-stripped to recover solvent and is then discarded.

The extracted glands are rendered to recover fat (and remove alcohol) and then are sold as animal feed protein. The precipitated protein containing filter aid is landfilled.

The hazardous wastes generated in this process are the solvent concentrate (containing fats and oils) left behind when the aqueous alcohol is recovered in the solvent recovery system and the wastewater from insulin precipitation which may contain traces of zinc salts. (Treatment of this wastewater with alkali would precipitate any zinc as the hydroxide which can then be removed by filtration.)

### 3.2.1.2.6 Biologicals

The biological products listed in SIC code 2831 include vaccines, toxoids, serum, and human blood fractions. The vaccines (such as influenza vaccine) are produced by growing virus mutants in chicken egg embryos, extracting the egg with a salt solution, and precipitating the active antigen with ammonium sulfate for use in vaccine production. Most toxoid production today is effected by tissue cell culture of the virus, followed by formaldehyde treatment of the culture medium to give the toxoid. Salk-type poliomyelitis toxoid is produced by this method.

Tetanus antiserum is produced from the blood of a horse that has been infected with the tetanus organism. While the horse itself remains healthy and active, tetanus antibodies are produced in its bloodstream.

Human blood plasma contains a series of protein fractions that have commercial medicinal use. Included in these protein fractions are antihemophilic globulin (to arrest severe hemorrhaging), gamma-globulins (for prevention of hepatitis, measles, chicken pox, and tetanus), thrombin (for blood coagulation), and albumin (for treating shock).

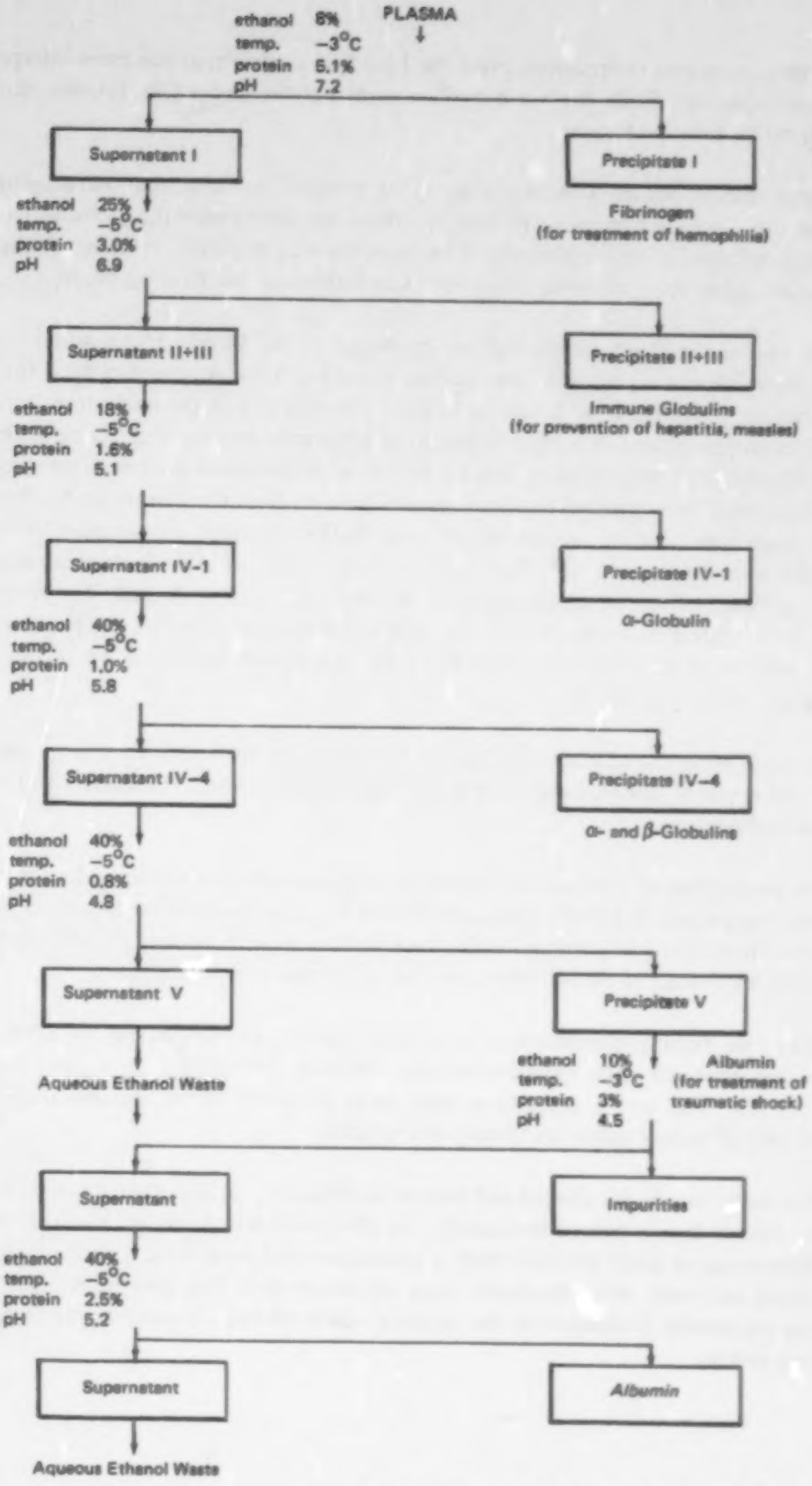
The two major classes of biologicals produced in the United States today are virus vaccines from chicken egg embryos and human blood fractions. A typical process for human blood fraction production is described below. Whole blood is received from donors (or obtained from placentas following childbirth) and the cells are removed (by centrifugation) to yield plasma. The sterile plasma may be used as is, or processed further to produce blood protein fractions. These protein fractions are precipitated from the plasma at -5°C by adding ethanol containing sodium acetate-acetic acid buffer in steps to increase the ethanol concentration and lower the pH. The number of steps and pH at each stage are dependent on the "method" of fractionation used and the protein fractions desired. The final step of Method 6 (outlined in Figure 3.2.1.2.6) is precipitation of albumin at pH 5.2 and 40% ethanol. Following this final precipitation, there is generally less than 2% of the original plasma protein left in solution.

The cells from the whole blood can be removed and discarded; they are removed for recovery of erythrocytes (red cells) for therapeutic treatment or, as in more recent practice, returned to the donor.

The production of commercial quantities of plasma protein fractions does not require very large equipment. A typical fractionation facility may handle a batch size of 500 liters of plasma (from over 1500 donors) with a maximum in-process volume of 2000 liters. From 1943-1963, an average of 50,000 liters per year of plasma were fractionated.

After the final precipitation, the diluted plasma contains about 40% ethanol by volume, less than 1% salts (sodium acetate, chloride, phosphate, carbonate) and about 0.03% protein. This would generate a total waste stream of about 240,000 liters (60,000 gal.) per year of watery waste containing 40% ethanol.

This waste can be (1) diluted and treated biologically, (2) the ethanol can be recovered and the residual liquor treated biologically, or (3) concentrated and incinerated. About 12 kg of diatomaceous earth per 500 liters of plasma are also used in this process as filter aid. If placentas are used, when discarded, they are incinerated. The other unwanted solids or solutions are usually discharged to the sanitary sewer and are handled by the liquid waste treatment system.



ethanol 8%
temp. −3°C
protein 5.1%
pH 7.2
PLASMA
Supernatant I
Precipitate I
Fibrinogen
(for treatment of hemophilia)
ethanol 25%
temp. −5°C
protein 3.0%
pH 6.9
Supernatant II+III
Precipitate II+III
Immune Globulins
(for prevention of hepatitis, measles)
ethanol 18%
temp. −5°C
protein 1.6%
pH 5.1
Supernatant IV−1
Precipitate IV−1
α-Globulin
ethanol 40%
temp. −5°C
protein 1.0%
pH 5.8
Supernatant IV−4
Precipitate IV−4
α- and β-Globulins
ethanol 40%
temp. −5°C
protein 0.8%
pH 4.8
Supernatant V
Precipitate V
Aqueous Ethanol Waste
ethanol 10%
temp. −3°C
protein 3%
pH 4.5
Albumin
(for treatment of traumatic shock)
Supernatant
Impurities
ethanol 40%
temp. −5°C
protein 2.5%
pH 5.2
Supernatant
Albumin
Aqueous Ethanol Waste

**Source:** A. Standen, Kirk-Othmer Encyclopedia of Chemical Technology. (See Bibliography)

FIGURE 3.2.1.2.6 DIAGRAMMATIC REPRESENTATION OF METHOD 6 BLOOD FRACTIONATION

### *3.2.1.3 Pharmaceutical Preparations (SIC 2834)*

Pharmaceuticals are prepared in dosage forms such as tablets, capsules, liquids, or ointments from the bulk pharmaceuticals and biologicals of SIC codes 2833 and 2831 and from other purchased raw materials. The methods used to manufacture these dose forms of pharmaceuticals are described below:

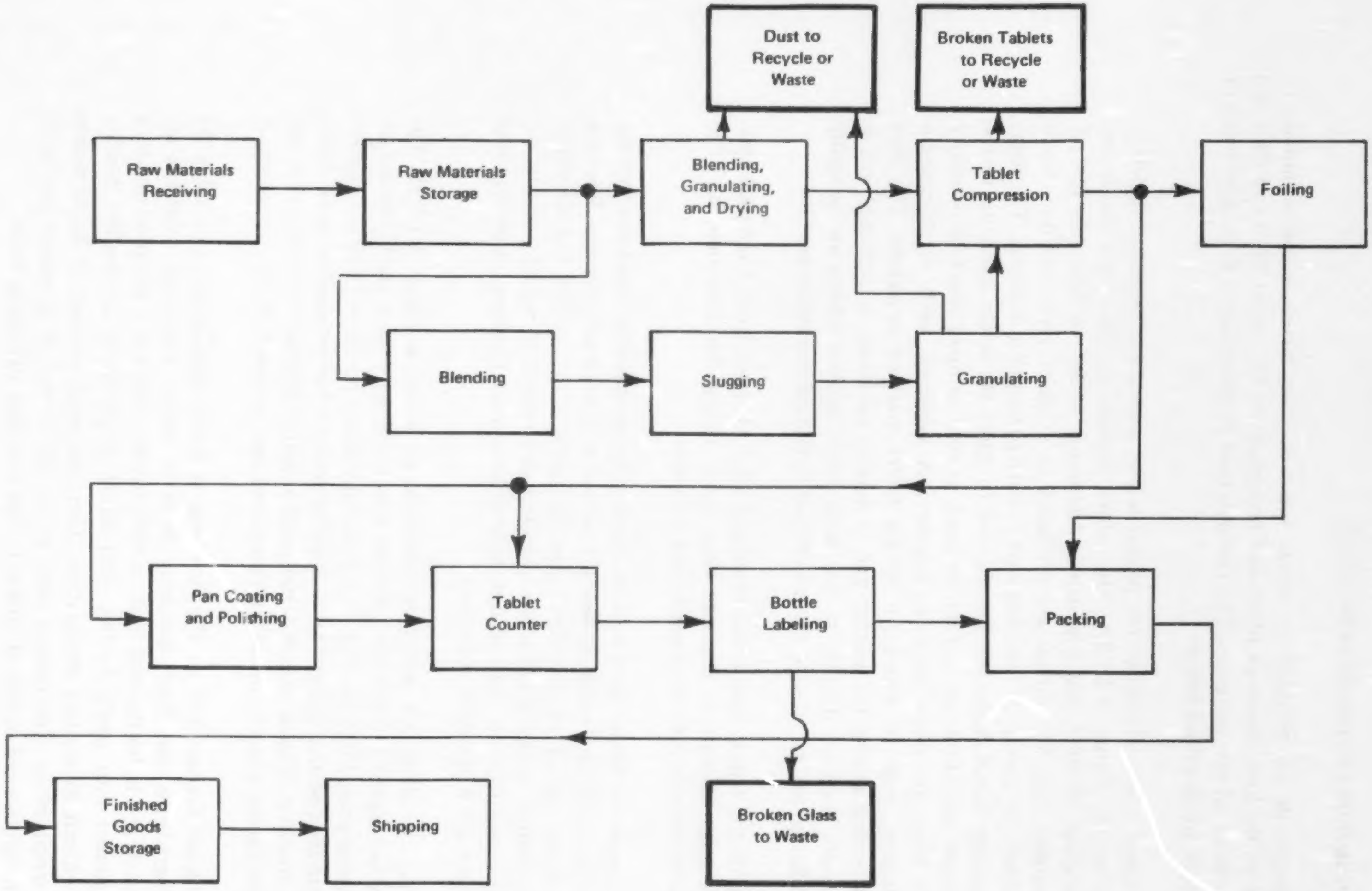
- *Tablets* – The flowsheet for production of coated and uncoated tablets is shown in Figure 3.2.1.3A. The active ingredient, filler, and binder are weighed, blended, and granulated. Additional binder, or filler, is added, if required, and the tablets are produced in a tablet press machine. Some tablets are coated by tumbling with a coating material and drying. The filler, (usually starch, sugar, etc.) is required to dilute the active medicinal to the proper concentration, and binder (such as corn syrup or starch) is necessary to bind the tablet particles together. A lubricant, such as magnesium stearate, may be added for proper tablet machine operation. The dust generated during the mixing and tabletting operation is collected and is usually recycled directly in the same batch. Broken tablets are generally collected and recycled to the granulation operation in a subsequent lot.

  After the tablets have been coated and dried, they are bottled and packaged. A small amount of breakage does occur during this operation, and this does generate some nonhazardous solid waste.

- *Capsules* – Empty hard gelatine capsules are produced by machines that dip rows of rounded metal dowels into a molten gelatine solution and then strip the capsules from the dowels after the capsules have cooled and solidified. Imperfect empty capsules are remelted and reused, if possible, or sold for glue manufacture. Most pharmaceutical companies purchase empty capsules from a few specialist producers.

  Capsule filling and packaging operations are shown in Figure 3.2.1.3B. The active ingredient and any filler are mixed and sometimes granulated before being poured into the empty gelatine capsules by machine. The filled capsules are then bottled and packaged. As in the case of tablet production, some dust is generated. This is recycled and small amounts disposed of. Some glass and packaging waste from broken bottles and cartons results from this operation.

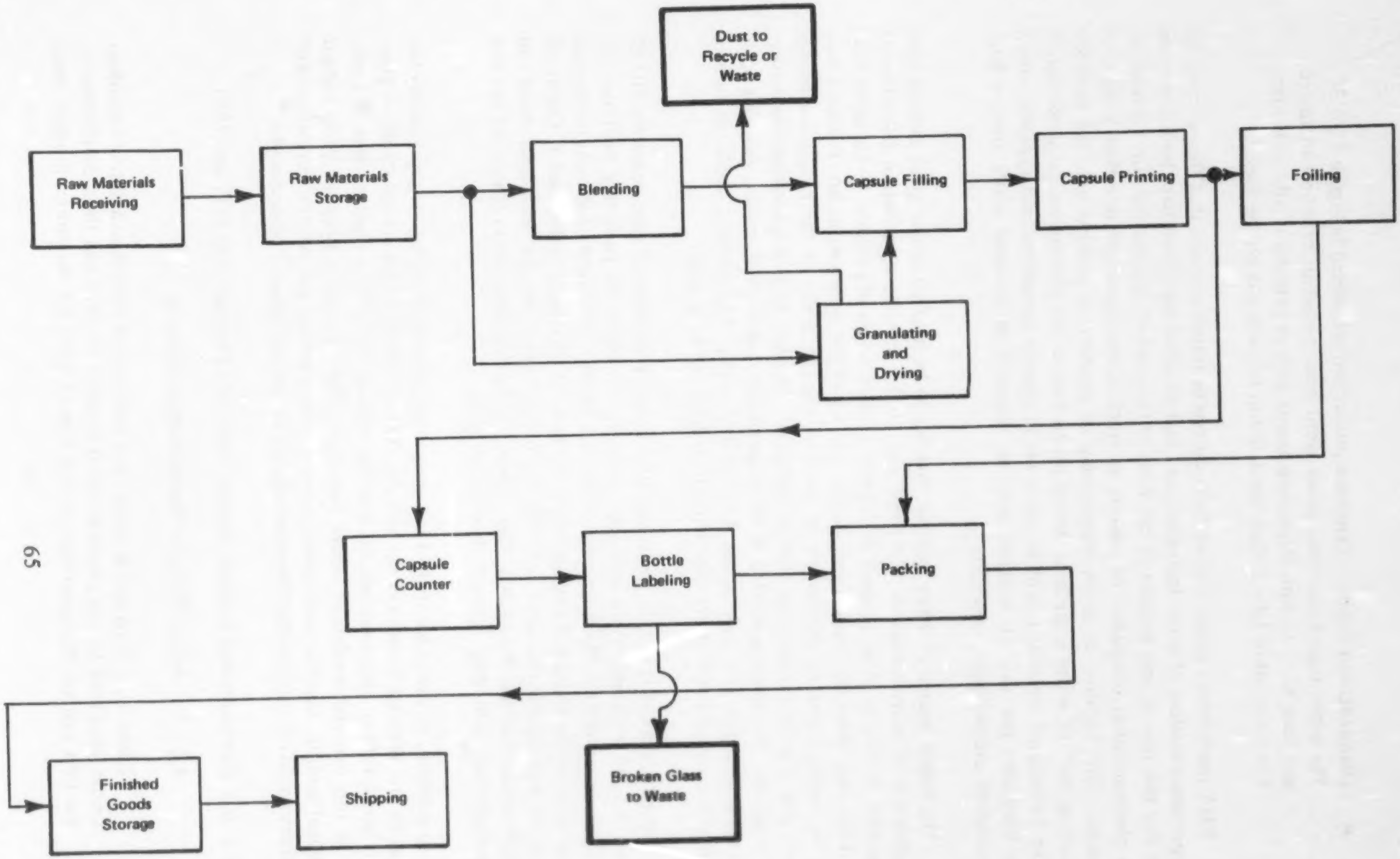
- *Liquid Preparations* – The first step in liquid preparation is weighing the ingredients and then dissolving them in water. Injectable solutions are packaged in bottles and heat- or bulk-sterilized by sterile filtration and then poured into sterile bottles. Oral liquid preparations are bottled directly without subsequent sterilization. There are small amounts of liquid wastes generated in this process that go to the sewer. Solid wastes are non-hazardous and consist of broken bottles and some packaging waste.


Raw Materials Receiving
Raw Materials Storage
Blending, Granulating, and Drying
Dust to Recycle or Waste
Broken Tablets to Recycle or Waste
Tablet Compression
Foiling
Blending
Slugging
Granulating
Pan Coating and Polishing
Tablet Counter
Bottle Labeling
Packing
Finished Goods Storage
Shipping
Broken Glass to Waste

● Indicates Start of Alternate Process.

**Source:** Arthur D. Little, Inc.

FIGURE 3.2.1.3-A PHARMACEUTICAL TABLET PRODUCTION


Raw Materials Receiving
Raw Materials Storage
Blending
Dust to Recycle or Waste
Capsule Filling
Capsule Printing
Foiling
Granulating and Drying
Capsule Counter
Bottle Labeling
Packing
Finished Goods Storage
Shipping
Broken Glass to Waste

● Indicates Start of Alternate Process.

**Source:** Arthur D. Little, Inc.

FIGURE 3.2.1.2-B PHARMACEUTICAL CAPSULE PRODUCTION

- *Ointments and Salves* – Ointment production is outlined in Figure 3.2.1.3C. The active ingredients (zinc oxide, antibiotic, cortisone, or other) are mixed and then blended with thickening agents such as petroleum jelly or lanolin. The ointment or salve is then injected into tubes or jars and packaged.

FDA regulations require that all formulations be tested to assure that they contain the proper concentration of active ingredient, and that all active ingredient have been accounted for. For this reason, and because of the value of the product, a concerted effort is made by the pharmaceutical companies to convert as much active ingredient into final product as possible. This requires as much reprocessing of product as possible and the complete "running out" of active ingredient during production of the pharmaceutical preparations. Some formulated material is sent to the sewer in cleanup operations, but typically only a few kilograms per day of material may be disposed of as solid waste from a large formulation and packaging operation.

The largest source of waste material that has to be handled at any given time is from recalled lots of pharmaceuticals. The recall may be due to company action in discontinuing a product, or due to some product deficiency, such as a loss of potency. In the latter case, the FDA may enter the picture and require a recall of the questionable lot. Products may also be recalled due to mislabeling or product mixups. Some of the recalls are readily correctable and the product can then be reshipped. In other cases it is necessary to destroy the entire lot. The waste generated in these operations is about 85% broken glass and waste packaging materials and only about 15% product waste. The product waste, in turn, is estimated to contain only about 20% active ingredient on the average.

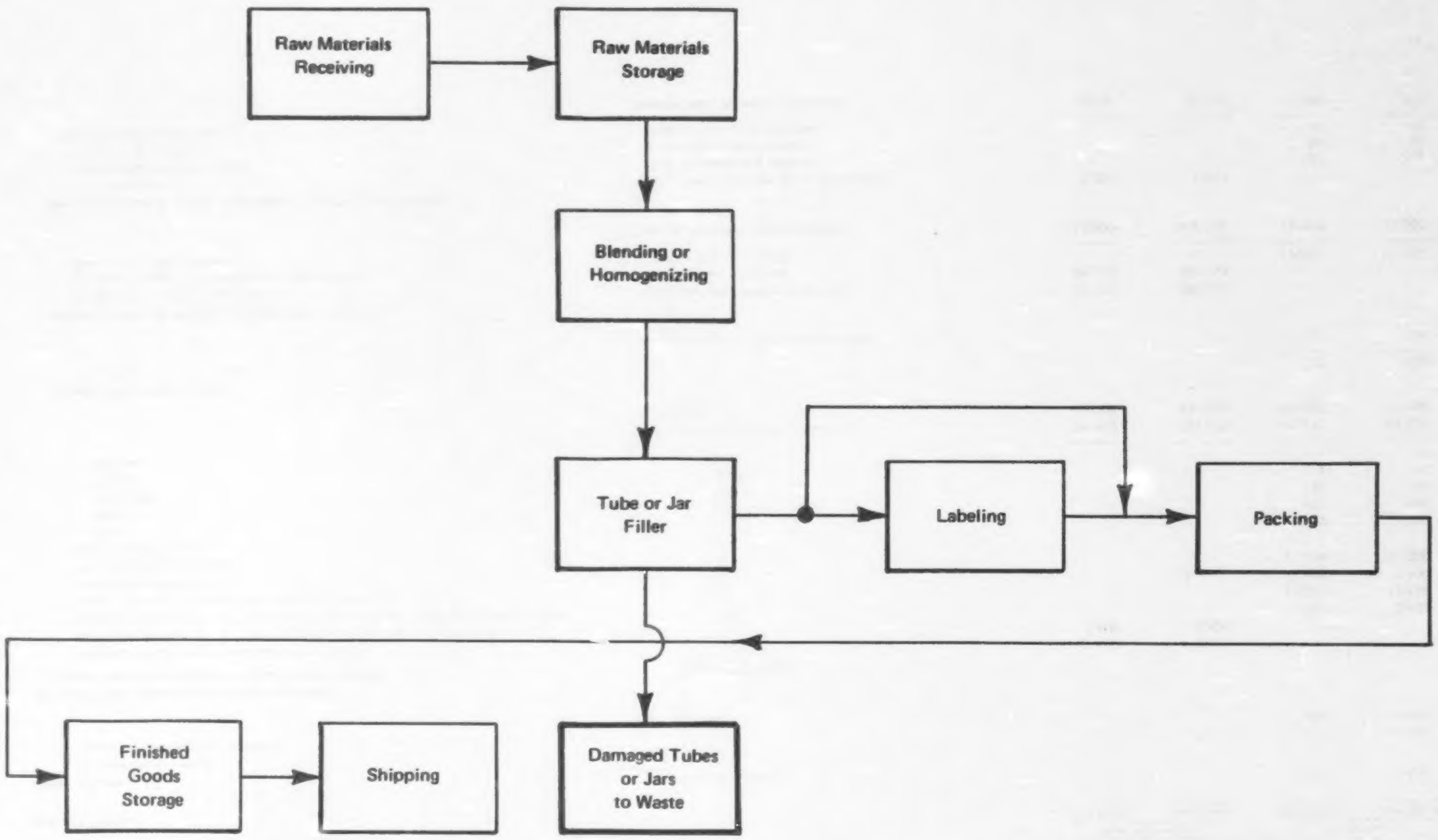
We estimate that the U.S. pharmaceutical industry disposes of approximately 10,000 metric tons of returned goods annually, primarily consisting of packaging materials and dilute active ingredient. There are also occasional batches of material that must be rejected due to cross-contamination, decomposition, and so forth, that must be disposed of. Certain of the active ingredients and some formulations in bulk form may be hazardous enough to warrant special disposal. We estimate that approximately 500 metric tons per year fall into this hazardous category for disposal from plants in SIC 2834.

In addition, we estimated that 75,000 metric tons of general rubbish are produced by the packaging and shipping sections of the industry. These rubbish wastes consist mostly of glass, paper, wood, rubber, aluminum and the like. We estimate that only a small fraction of 1 percent of this material consists of active ingredient. The material is disposed of in regular municipal landfills, together with cafeteria wastes, office wastes, and so forth. For purposes of this study we do not consider that this waste should be categorized as a "process waste."

### *3.2.1.4 U.S. Pharmaceutical Industry Process Wastes and Projections to 1977 and 1983*

#### 3.2.1.4.1 Annual Waste of Pharmaceutical Industry

Tables 3.2.1.4.1A and B present our estimates of hazardous and non-hazardous wastes generated by the pharmaceutical industry in 1973 and their distribution in the EPA regions. The quantities of each type of waste for the various products were


Raw Materials Receiving
Raw Materials Storage
Blending or Homogenizing
Tube or Jar Filler
Labeling
Packing
Finished Goods Storage
Shipping
Damaged Tubes or Jars to Waste

● Indicates Start of Alternate Process.

Source: Arthur D. Little, Inc.

FIGURE 3.2.1.3-C PHARMACEUTICAL OINTMENT PRODUCTION

## TABLE 3.2.1.4.1.A

## PHARMACEUTICAL INDUSTRY WASTE GENERATION ESTIMATE FOR 1973[1]

| Industry Segment | | Metric Tons Waste (1973) | | | |
|---|---|---|---|---|---|
| | | Non-Hazardous | | Hazardous | |
| | | Dry Basis | Wet Basis | Dry Basis | Wet Basis * |
| **R&D** Solvent | 66 liters/researcher | – | – | 1,500 | 1,500 |
| Animals (Incinerated) | | – | – | – | – |
| Heavy Metals (Contract Disposal) | | – | – | <1 | <1 |
| | Total for R&D | – | – | 1,500 | 1,500 |
| **SIC Code 2833: Production of Active Ingredients** | | | | | |
| **Organic Medicinal Chemicals (34,000 Metric Tons/Yr)** | Tons/Ton Product | | | | |
| Biological Sludge (from Wastewater Treatment) | 1.4 | 47,800 | 476,000 | | |
| High Inert Content Waste – Non-Hazardous (Filter aid, activated carbon) | 0.1 | 3,400 | 6,800 | | |
| High Inert Content Waste – Hazardous (Contaminated filter aid, activated carbon) | 0.05 | | | 1,700 | 3,400 |
| Organic Chemical Residue (Tars, muds, still bottoms) | 0.4 | | | 13,600 | 13,800 |
| Halogenated Solvent | 0.1 | | | 3,400 | 3,400 |
| Non-Halogenated Solvent | 0.7 | | | 23,800 | 23,800 |
| Heavy Metal Wastes | | | | | |
| Zinc | 0.070 | | | 2,200 | 2,200 |
| Arsenic | 0.015 | | | 450 | 450 |
| Chromium | 0.001 | | | 20 | 20 |
| Copper | <0.001 | | | 4 | 4 |
| Mercury | <0.001 | | | 1 | 1 |
| | Total for Organic Medicinal Chemicals | 51,000 | 482,800 | 45,175 | 46,875 |
| | Rounded to | 51,000 | 480,000 | 45,000 | 47,000 |
| **Inorganic Medicinal Chemicals** | | | | | |
| Heavy Metals (i.e., selenium) | | | | 200 | 200 |
| | Total for Inorganic Medicinal Chemicals | | | 200 | 200 |
| **Antibiotics (by Fermentation, 10,000 Metric Tons/Yr)** | | | | | |
| Mycelium (plus filter aid and sawdust) | 7.5 tons (dry wt)/ton antibiotic | 75,000 | 300,000 | – | – |
| Biological Sludge (from wastewater treatment) | 3.5 tons/ton antibiotic | 35,000 | 350,000 | – | – |
| Waste Solvent Concentrate | 1.2 tons/ton antibiotic | – | – | 12,000 | 12,000 |
| | Total for Fermentation (Antibiotics) | 110,000 | 650,000 | 12,000 | 12,000 |
| **Botanicals (Plant Alkaloids, 2,000 Metric Tons/Yr Plant Material)** | | | | | |
| Wet Plant Material | 1 ton (dry basis) per ton plant material | 2,000 | 4,000 | – | – |
| Aqueous Solvent Concentrate | 0.36 ton/ton plant material | – | – | 720 | 850 |
| Halogenated Solvent | 0.03 ton/ton plant material | – | – | 60 | 60 |
| Non-Halogenated Solvent | 0.06 ton/ton plant material | – | – | 120 | 120 |
| | Total for Plant Alkaloids (Botanical) | 2,000 | 4,000 | 900 | 1,030 |

## TABLE 3.2.1.4.1.A (Continued)

| Industry Segment | | Metric Tons Waste (1973) | | | |
|---|---|---|---|---|---|
| | | Non-Hazardous | | Hazardous | |
| | | Dry Basis | Wet Basis | Dry Basis | Wet Basis* |
| **Botanicals (Plant Steroids, 150 Metric Tons/Yr Stigmasterol)** | | | | | |
| Fused Plant Steroid Ingots | 5 tons/ton stigmasterol | 750 | 750 | – | – |
| | Total for Plant Steroids | 750 | 750 | – | – |
| **Medicinals from Animal Glands (8000 Metric Tons Glands/Yr)** | | | | | |
| | Tons/Ton Animal Glands | | | | |
| Extracted Animal Tissue | 0.940 | 7,500 | 7,500 | – | – |
| Fats or Oils | 0.044 | 350 | 350 | – | – |
| Filter Cake (contains precipitated protein) | 0.031 | 250 | 500 | – | – |
| Aqueous Solvent Concentrate | 0.100 | – | – | 800 | 1,600 |
| | Total for Medicinals from Animal Glands | 8,100 | 8,350 | 800 | 1,600 |
| | Total for Production of Active Ingredients (SIC Code 2833) | 172,000 | 1,143,000 | 58,000 | 62,000 |
| **SIC Code 2831: Biological Products** | | | | | |
| Aqueous Ethanol Waste from Blood Fractionation | 5 liters/liter plasma | – | – | 250 | 600 |
| Antiviral Vaccine | | – | – | 300 | 300 |
| Other Biologicals (Toxoids, serum) | | – | – | 200 | 200 |
| | Total for Biological Products SIC Code 2831 | – | – | 750 | 1,100 |
| **SIC Code 2834: Pharmaceutical Preparations (Formulation, Packaging and Returns)** | | | | | |
| Total Returned Goods (Primarily packaging material and dilute active ingredient) | | 10,000 | 10,000 | – | – |
| Contaminated or Decomposed Active Ingredient | | – | – | 500 | 500 |
| | Total for Pharmaceutical Preparations | 10,000 | 10,000 | 500 | 500 |
| | Totals for all Industry Segments | 181,850 | 1,153,000 | 61,650 | 65,100 |
| | Rounded to: | 182,000 | 1,153,000 | 62,000 | 65,000 |

*Wet weight estimates are given for all wastes. The two wastes that typically have the highest moisture content are biological sludge and mycelium from fermentations. Where the wet waste estimates are the same as on the dry basis, the waste is usually disposed of with only a minor amount of moisture. However, disposal practices vary from plant to plant, depending on the form in which the waste is produced.

†Source: Arthur D. Little, Inc., estimates.

## TABLE 3.2.1.4.1B

## DISTRIBUTION OF PHARMACEUTICAL INDUSTRY WASTE GENERATION (1973)[†]

Metric Tons Waste

| Industry Segment | Waste Type | Regions I & II | | Region III | | Region IV | | Region V | | Region VI | | Region VII | | Region VIII | | Region IX | | Region X | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. | Non-Haz. | Haz. |
| R&D | Solvent | — | 780 | — | — | — | — | — | 420 | — | 60 | — | 60 | — | — | — | 180 | — | — | — | 1,500 |
| Synthetic Organic Medicinals | Biological Sludge | 28,600 | — | 4,800 | — | 4,800 | — | 7,100 | — | 400 | — | 700 | — | — | — | 1,200 | — | — | — | 47,600 | — |
| | Inert Wastes | 2,000 | — | 300 | — | 300 | — | 500 | — | 50 | — | 100 | — | — | — | 150 | — | — | — | 3,400 | — |
| | Contam. Inerts | — | 1,000 | — | 150 | — | 150 | — | 200 | — | — | — | 100 | — | — | — | 100 | — | — | — | 1,700 |
| | Halogenated Solvents | — | 2,000 | — | 300 | — | 300 | — | 500 | — | 50 | — | 100 | — | — | — | 150 | — | — | — | 3,400 |
| | Non-Halogenated Solvent | — | 14,300 | — | 2,400 | — | 2,400 | — | 3,600 | — | 150 | — | 350 | — | — | — | 600 | — | — | — | 23,800 |
| | Organic Residues | — | 8,200 | — | 1,400 | — | 1,400 | — | 2,100 | — | 50 | — | 150 | — | — | — | 300 | — | — | — | 13,600 |
| Fermentation (Antibiotics) | Mycelia (Dry Basis) | 34,000 | — | 7,500 | — | — | — | 30,000 | — | — | — | 1,000 | — | — | — | 2,500 | — | — | — | 75,000 | — |
| | Biological Sludge | 15,000 | — | 3,600 | — | — | — | 14,000 | — | — | — | 700 | — | — | — | 1,700 | — | — | — | 35,000 | — |
| | Waste Solvent Concen. | — | 5,000 | — | 1,200 | — | — | — | 4,800 | — | — | — | 200 | — | — | — | 800 | — | — | — | 12,000 |
| Botanicals | Plant Material | 1,200 | — | 200 | — | 200 | — | 300 | — | — | — | — | — | — | — | 100 | — | — | — | 2,000 | — |
| | Aqueous Solvent | — | 420 | — | 100 | — | 50 | — | 100 | — | — | — | — | — | — | — | 50 | — | — | — | 720 |
| | Halogenated Solvent | — | 30 | — | 10 | — | 5 | — | 10 | — | — | — | — | — | — | — | 5 | — | — | — | 60 |
| | Non-Halogenated Solvent | — | 60 | — | 20 | — | 10 | — | 20 | — | — | — | — | — | — | — | 10 | — | — | — | 120 |
| Fused Plant Steroids | Distribution Not Determined | | | | | | | | | | | | | | | | | | | 700 | — |
| Animal Source | Animal Tissue | 4,400 | — | 740 | — | 740 | — | 1,200 | — | — | — | 200 | — | — | — | 220 | — | — | — | 7,500 | — |
| | Fats or Oils | 200 | — | 35 | — | 35 | — | 50 | — | — | — | 15 | — | — | — | 15 | — | — | — | 350 | — |
| | Filter Cake | 140 | — | 30 | — | 30 | — | 40 | — | — | — | 5 | — | — | — | 5 | — | — | — | 250 | — |
| | Aqueous Solvent | — | 500 | — | 80 | — | 80 | — | 120 | — | — | — | 50 | — | — | — | 70 | — | — | — | 900 |
| Biologicals | Waste Solvent | — | 25 | — | 25 | — | 25 | — | 60 | — | — | — | 50 | — | — | — | 65 | — | — | — | 250 |
| | Other | — | 50 | — | 50 | — | 50 | — | 120 | — | — | — | 100 | — | — | — | 130 | — | — | — | 500 |
| Formulation, Packaging, Returned Goods | Returned Goods | 4,400 | — | 1,100 | | 1,000 | — | 1,800 | — | 300 | — | 500 | — | — | — | 900 | — | — | — | 10,000 | — |
| | Active Ingredient | — | 220 | — | 60 | — | 50 | — | 90 | — | 15 | — | 25 | — | — | — | 40 | — | — | — | 500 |
| Heavy Metal Wastes from Organic and Inorganic Medicinal Production | Distribution Not Determined | | | | | | | | | | | | | | | | | | | | 2,900 |
| | Totals for All Industry Segments | | | | | | | | | | | | | | | | | | | 181,850 | 81,850 |
| | Rounded to: | | | | | | | | | | | | | | | | | | | 182,000 | 82,000 |

Legend: Non-Haz. = Non Hazardous
Haz. = Hazardous

[†] Source: Arthur D. Little, Inc., estimates.

extrapolated to an annual (1973) basis from data gathered at the plants visited using the following three methods:

1. Production of a given pharmaceutical product at the plants visited compared to total industry production in the United States;
2. Value of production of a pharmaceutical product at the plants visited as a percentage of annual total value of that product in the United States; and
3. Generation of a given waste as related to total value of production or number of production employees.

We estimated the total annual quantity of solvent waste originating from R&D operations on the basis of quantities generated per researcher at the facilities we visited. Since test animals are routinely incinerated on-site and the amount of heavy metal waste is very small and disposed of by waste disposal contractors, we did not include figures for these wastes in this table.

The production of organic medicinal chemicals creates waste solvents, chemical tars and residues, wet filter aid or carbon, some heavy metal waste, and biological sludge from on-site or off-site biological treatment of water-soluble organic compounds, such as acetic acid or alcohol. The wet filter aid or carbon may be non-hazardous or may contain contaminating materials such as solvent, corrosives or heavy metals that render it hazardous. (The heavy metal contents of the heavy metal wastes listed in Table 3.2.1.4.1A were presented earlier in Table 3.2.1.2.1.) Many pharmaceutical companies also produce crude antibiotics and growth stimulants such as arsanilic acid for the animal feed industry, but these products are not listed as part of SIC code 2833. Several companies are also producers of some heavy chemical fermentation products, such as citric and itaconic acid, but these again are not part of SIC code 2833.

Inorganic, medicinal, chemical, active-ingredient production usually generates non-hazardous aqueous waste salt solution and little or no solid hazardous waste. In addition, a large portion of the active ingredients for manufacture of inorganic medicinals is purchased from the heavy chemicals industry.

Fermentation is used for the production of most crude antibiotics, for chemical conversion of some steroids, and for the production of some industrial heavy chemicals. The fermentation, product recovery, and purification processes result in considerable quantities of non-hazardous wastes, such as mycelia and spent nutrient broth. The main hazardous waste generated is a solvent concentrate. This waste contains organics from recovery of solvent used in the product recovery and purification sections of the process. The weight of dry mycelia waste per ton of product is considerably higher for other antibiotics than it is for penicillin, since it is necessary to use a significant amount of filter aid to remove the mycelia from the broth and the yields of some of the other antibiotics per ton of mycelia is lower. Some State regulations also require a minimum solids content of the mycelia waste for landfill disposal, so an additional filter such as sawdust must be added to increase the solids content.

The extraction of botanicals, such as roots and leaves, and animal organs, such as pancreas glands or lung tissue for alkaloid, steroid, and hormone products, respectively, is usually accomplished using acidic aqueous alcohol and often requires a second halogenated solvent in the purification process. These solvents are recovered for reuse, thus generating a waste solvent concentrate. The wet botanicals are disposed of by landfill, but the animal organ by-products (extracted glands and fats) are sold when possible.

The quantities of returned goods and active ingredients disposed of were projected as being proportional to the total value of production.

The major wastes generated in the production of biologicals include aqueous alcohol and dissolved salts from human blood plasma fractions and formaldehyde-egg waste from antiviral production. There is a limited amount of production of other biologicals, such as horse serum products and toxoids, but the total production of biologicals is quite small compared to the production of other pharmaceuticals.

Heavy metal wastes occur mostly in the production of organic medicinal chemicals. In some cases, such as the selenium waste, the waste stream is unique to one process and one manufacturer. In other cases, there are several producers that have a similar waste heavy metal (mercurials), and yet other heavy metal wastes, such as zinc compounds, are found throughout the industry. This factor was taken into consideration in estimating the annual generation of each of these heavy metal wastes.

In Table 3.2.1.4.1B we have apportioned the waste generation figures for the whole United States, as listed in Table 3.2.1.4.1A, among the various EPA regions. Our estimates of waste generation distribution are based on production figures for antibiotics, synthetic organic medicinals, and biologicals of the pharmaceutical companies in these regions. Waste generation from R&D facilities was estimated from PMA data showing locations of R&D personnel. Location of major formulation and packaging facilities was used to estimate distribution of returned goods. Regions I and II were combined in Table 3.2.1.4.1B to avoid disclosure of confidential information on production or waste stream data on plants in Region I which has only one large plant in SIC 2833.

Waste generation on a state-by-state basis is presented in Table 3.2.1.4.1C. Regional and national totals are also given. State totals for heavy metals are not estimated because of the difficulty in estimating the specialized use of these materials in individual plants. State estimates for mycelium waste generation have also been omitted, because only 16 major fermentation installations produce antibiotics in the continental United States. Seven states have only one plant each, one state has two, one state has three, and only one state has four major plants. Again, state-by-state figures on mycelium production would divulge confidential information on several companies. Many states have so few people employed in the pharmaceutical industry that the waste is considered insignificant, and blanks therefore appear in the table. The reason for the spotty distribution is apparent when one considers that SIC code 2833 (which contributes almost all the hazardous and nonhazardous waste from the industry) contains only 54 installations that have more than 20 employees each.

# TABLE 3.2.1.4.1C

## ESTIMATED DISTRIBUTION OF WASTE GENERATED BY THE PHARMACEUTICAL INDUSTRY IN 1973

(annual metric tons – dry basis)

| | | Hazardous | | | | | | | Non-Hazardous | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | State | Halogenated[1] Solvent Waste | Non-Halogenated Solvent Waste | Organic[2] (Chemical) Residues | Contaminated[3] High Inerts Waste | Active Ingredient | Heavy Metals | Total Hazardous* | Biological[4] Sludge | Plant Material[5] Animal Tissue Fats, Oil | High Inerts[3,6] Waste (Non-Haz.) | Returned Goods | Mycelium[7] | Total Nonhazardous* |
| IV | Alabama | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Alaska | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IX | Arizona | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Arkansas | – | – | – | – | – | – | – | 90 | – | 10 | 70 | – | 170 |
| IX | California | 330 | 1,600 | 430 | 100 | 40 | – | 2,500 | 2,900 | 330 | 150 | 900 | – | 4,280 |
| VIII | Colorado | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Connecticut | 200 | 1,400 | 500 | 100 | 20 | – | 2,220 | 3,000 | 400 | 100 | 300 | – | 3,800 |
| III | Delaware | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Florida | 40 | 400 | 250 | 25 | 5 | – | 720 | 500 | 100 | 30 | 100 | – | 730 |
| IV | Georgia | 60 | 500 | 200 | 25 | 5 | – | 790 | 500 | 100 | 30 | 100 | – | 730 |
| IX | Hawaii | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Idaho | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Illinois | 300 | 2,900 | 760 | 70 | 30 | – | 4,060 | 7,000 | 520 | 180 | 650 | – | 8,350 |
| V | Indiana | 330 | 3,100 | 810 | 70 | 30 | – | 4,340 | 7,600 | 540 | 190 | 600 | – | 8,930 |
| VII | Iowa | 30 | 130 | 50 | 20 | 5 | – | 235 | 700 | 110 | 50 | 100 | – | 960 |
| VII | Kansas | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Kentucky | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Louisiana | 10 | 10 | 5 | – | – | – | 25 | 40 | – | 10 | 30 | – | 80 |
| I | Maine | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Maryland | – | – | – | – | – | – | – | 600 | 70 | 20 | 80 | – | 770 |
| I | Massachusetts | – | – | – | – | – | – | – | 600 | 100 | 100 | 100 | – | 900 |
| V | Michigan | 200 | 1,900 | 450 | 40 | 20 | – | 2,610 | 4,600 | 340 | 120 | 400 | – | 5,460 |
| V | Minnesota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Mississippi | – | – | – | – | – | – | – | 800 | 200 | 50 | 200 | – | 1,250 |
| VII | Missouri | 110 | 440 | 170 | 70 | 20 | – | 810 | 700 | 70 | 35 | 300 | – | 1,105 |
| VIII | Montana | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VII | Nebraska | 20 | 80 | 30 | 10 | – | – | 140 | – | 35 | 20 | 100 | – | 155 |
| IX | Nevada | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | New Hampshire | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New Jersey | 1,600 | 11,000 | 4,700 | 500 | 120 | – | 17,920 | 24,200 | 3,200 | 1,140 | 2,400 | – | 30,940 |
| VI | New Mexico | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New York | 800 | 6,000 | 2,300 | 300 | 60 | – | 9,460 | 12,000 | 1,600 | 600 | 1,200 | – | 15,400 |
| IV | North Carolina | 100 | 900 | 550 | 50 | 20 | – | 1,620 | 1,500 | 300 | 120 | 300 | – | 2,220 |
| VIII | North Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Ohio | 70 | 600 | 150 | 10 | 10 | – | 840 | 1,500 | 110 | 40 | 120 | – | 1,770 |
| VI | Oklahoma | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Oregon | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Pennsylvania | 270 | 3,300 | 1,250 | 130 | 50 | – | 5,000 | 6,500 | 800 | 250 | 850 | – | 8,400 |
| II | Puerto Rico | 200 | 2,000 | 750 | 100 | 20 | – | 3,070 | 3,800 | 500 | 200 | 400 | – | 4,900 |
| I | Rhode Island | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | South Carolina | – | – | – | – | – | – | – | 500 | 100 | 20 | 100 | – | 720 |
| VIII | South Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Tennessee | 100 | 800 | 450 | 50 | 20 | – | 1,420 | 1,000 | 200 | 80 | 200 | – | 1,480 |
| VI | Texas | 100 | 140 | 45 | – | 15 | – | 300 | 270 | – | 30 | 200 | – | 500 |
| VIII | Utah | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Vermont | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Virginia | 40 | 550 | 200 | 20 | 10 | – | 820 | 1,100 | 100 | 50 | 140 | – | 1,390 |
| X | Washington | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | West Virginia | – | – | – | – | – | – | – | 200 | 30 | 10 | 30 | – | 270 |
| V | Wisconsin | 30 | 200 | 50 | 10 | – | – | 290 | 400 | 50 | 10 | 30 | – | 490 |
| VIII | Wyoming | – | – | – | – | – | – | – | – | – | – | – | – | – |
| | National Totals | 4,940 | 37,950 | 14,100 | 1,700 | 500 | 2,900 | 50,190 | 82,800 | 9,905 | 3,845 | 10,880 | 75,000 | 106,150 |
| | **Region Totals** | | | | | | | | | | | | | |
| | I | 200 | 1,400 | 500 | 100 | 20 | – | 2,220 | 3,600 | 500 | 200 | 400 | – | 4,700 |
| | II | 2,600 | 19,000 | 7,750 | 900 | 200 | – | 30,450 | 40,000 | 5,300 | 1,940 | 4,000 | – | 51,240 |
| | III | 310 | 3,850 | 1,450 | 150 | 60 | – | 5,820 | 8,400 | 1,000 | 330 | 1,100 | – | 10,830 |
| | IV | 300 | 2,600 | 1,450 | 150 | 50 | – | 4,550 | 4,800 | 1,000 | 330 | 1,000 | – | 7,130 |
| | V | 930 | 8,700 | 2,220 | 200 | 90 | – | 12,140 | 21,100 | 1,560 | 540 | 1,800 | – | 25,000 |
| | VI | 110 | 150 | 50 | – | 15 | – | 325 | 400 | – | 50 | 300 | – | 750 |
| | VII | 160 | 650 | 250 | 100 | 25 | – | 1,185 | 1,400 | 215 | 105 | 500 | – | 2,220 |
| | VIII | – | – | – | – | – | – | – | – | – | – | – | – | – |
| | IX | 330 | 1,600 | 430 | 100 | 40 | – | 2,500 | 2,900 | 330 | 150 | 900 | – | 4,280 |
| | X | – | – | – | – | – | – | – | – | – | – | – | – | – |

Notes:
1. Includes R&D solvent wastes.
2. Includes biological product organic wastes.
3. Dry wt x 2 = wet weight
4. Dry wt x 10 = wet weight
5. Dry wt x 1.2 = wet weight
6. Includes filter cake for animal source pharmaceuticals.
7. Dry wt x 4.35 = wet weight

*(excludes metals)

*(includes mycelium)

### 3.2.1.4.2 Typical Types of Pharmaceutical Hazardous Wastes and Their Properties

Table 3.2.1.4.2 lists the typical types of hazardous waste materials discharged from pharmaceutical operations. The physical, chemical, and biological properties of the hazardous constituents of these wastes are listed in Appendix B.

### 3.2.1.4.3 Projections of Pharmaceutical Process Wastes to 1977 and 1983.

Medicinal ingredient production in the United States has increased at an annual compounded rate of 6.3% for the past 20 years. Also, prescription numbers have been increasing at approximately the same rate. However, we note that production has sometimes slackened during recessions, and thus we anticipate that the present energy shortages and disruptions of the economy may have an adverse effect on medicinal ingredient production in the immediate future. We are therefore projecting waste increases on the basis of a 3 percent compounded rate until 1977. We expect passage of a National Health Care Act in 1976 and believe that growth will then be slightly above historical trends. We have therefore projected waste growth from 1977 to 1983 on the basis of a 7 percent compounded rate. Final effluent guidelines have not been set for the pharmaceutical industry. We examined the preliminary recommendations for the industry and concluded that the guidelines will not add to the tonnage of wastes to be landfilled from air and wastewater treatment processes. Projections of hazardous and non-hazardous wastes by industry segments for 1977 and 1983 are shown in Table 3.2.1.4.3A. The totals of hazardous and non-hazardous waste generated in 1973 and the waste generation factors for each waste (metric tons of waste per metric ton of product or raw material) were developed earlier in Table 3.2.1.4.1A and Section 3.2.1.2.1. The projected distribution of wastes by state was calculated from Table 3.2.1.4.1C by using the same 3 percent and 7 percent compounded rate referred to above. Estimates of state data for 1977 are presented in Table 3.2.1.4.3B and for 1983 in Table 3.2.1.4.3C. Due to rounding, totals of the various tables may not agree exactly.

## TABLE 3.2.1.4.2

## SUMMARY OF TYPICAL TYPES OF PHARMACEUTICAL HAZARDOUS WASTE MATERIALS[†]

**Antibiotics (Penicillin, Tetracyclines, Cephalosporins)**

- Recovery Solvents
  - Amyl acetate
  - Butanol
  - Butyl acetate
  - Methylisobutyl ketone
- Purification Solvents
  - Butanol
  - Acetone
  - Ethylene Glycol Monomethyl Ether

**Alkaloids (Quinine, Reserpine, Vincristine) from Plant Material**

- Extraction Solvents
  - Methanol
  - Acetone
  - Ethanol
  - Chloroform
  - Heptane
  - Ethylene Dichloride
- Purification Solvents
  - Ethylene Dichloride
  - Naphtha
  - Methylene Chloride
  - Benzene

**Crude Steroids from Plant Material**

- Still bottoms (Soybean Oil Residue)

**Medicinals from Animal Organs (Insulin, Heparin)**

- Ethanol
- Methanol
- Acetone

**Synthetic Organic Medicinals**

- Typical Solvents
  - Acetone
  - Toluene
  - Xylene
  - Benzene
  - Isopropyl alcohol
  - Methanol
  - Ethylene Dichloride
  - Acetonitrile
- Organic Residues (Still Bottoms, Sludges, Polymers, Tars)
  - Terpenes
  - Steroids
  - Vitamins
  - Tranquilizers
- Inert Solids (Generally Non-Hazardous)
  - Activated Carbon
  - Filter Aid
  - Filter Cloths
- Heavy Metals
  - Copper
  - Mercury
  - Arsenic
  - Selenium
  - Zinc
  - Chromium

**Blood Plasma Fractions**

- Solvent
  - Ethanol
- Salts
  - Sodium Acetate
  - Sodium Chloride
  - Sodium Phosphate

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[†] **Source:** Arthur D. Little, Inc., estimates.

## TABLE 3.2.1.4.3A

## ESTIMATES OF PHARMACEUTICAL INDUSTRY GENERATED WASTES FOR 1973, 1977 AND 1983*
(All Figures in Metric Tons Per Year)

| | 1973 | | | | 1977 | | | | 1983 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | |
| Industry Segment | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† |
| **R&D** | | | | | | | | | | | | |
| Solvent | – | – | 1,500 | 1,500 | – | – | 1,900 | 1,900 | – | – | 2,700 | 2,700 |
| Total R&D | – | – | 1,500 | 1,500 | – | – | 1,900 | 1,900 | – | – | 2,700 | 2,700 |
| **SIC Code 2833: Production of Active Ingredients** | | | | | | | | | | | | |
| **Organic Medicinal Chemicals (34,000 Metric Tons/Yr)** | | | | | | | | | | | | |
| Biological Sludge (from wastewater treatment) | 47,600 | 476,000 | – | – | 53,600 | 536,000 | – | – | 80,400 | 804,000 | – | – |
| High Inert Content (filter aid, carbon) | 3,400 | 6,800 | – | – | 3,800 | 7,600 | – | – | 5,700 | 11,400 | – | – |
| Contaminated High Inert Content (i.e., filter aid and solvent) | – | – | 1,700 | 3,400 | – | – | 1,900 | 3,800 | – | – | 2,900 | 5,800 |
| Organic Chemical Residues (tars, mud, still bottoms) | – | – | 13,600 | 13,600 | – | – | 15,300 | 15,300 | – | – | 23,000 | 23,000 |
| Halogenated Solvent | – | – | 3,400 | 3,400 | – | – | 3,800 | 3,800 | – | – | 5,700 | 5,700 |
| Non-Halogenated Solvent | – | – | 23,800 | 23,800 | – | – | 26,800 | 26,800 | – | – | 40,000 | 40,000 |
| Heavy Metal Wastes | | | | | | | | | | | | |
| Zinc Compounds | – | – | 2,200 | 2,200 | – | – | 2,500 | 2,500 | – | – | 3,700 | 3,700 |
| Arsenic Compounds | – | – | 450 | 450 | – | – | 500 | 500 | – | – | 750 | 750 |
| Chromium Compounds | – | – | 20 | 20 | – | – | 22 | 22 | – | – | 35 | 35 |
| Copper Compounds | – | – | 4 | 4 | – | – | 4 | 4 | – | – | 6 | 6 |
| Mercury Compounds | – | – | 1 | 1 | – | – | 1 | 1 | – | – | 1 | 1 |
| Total for Organic Medicinal Chemicals | 51,000 | 482,800 | 45,175 | 46,875 | 57,400 | 543,600 | 50,827 | 52,727 | 86,100 | 815,400 | 76,092 | 78,992 |
| Rounded to: | 51,000 | 480,000 | 45,000 | 47,000 | 57,000 | 540,000 | 51,000 | 53,000 | 86,000 | 815,000 | 76,000 | 79,000 |
| **Inorganic Medicinal** | | | | | | | | | | | | |
| Heavy Metals (i.e., selenium waste) | – | – | 200 | 200 | – | – | 225 | 225 | – | – | 350 | 350 |
| **Antibiotics (by Fermentation, 10,000 Metric Tons/Yr)** | | | | | | | | | | | | |
| Mycelium (plus filter aid and sawdust) | 75,000 | 300,000 | – | – | 84,400 | 338,000 | – | – | 127,000 | 508,000 | – | – |
| Biological Sludge | 35,000 | 350,000 | – | – | 39,400 | 394,000 | – | – | 60,000 | 600,000 | – | – |
| Waste Solvent Concentrate | – | – | 12,000 | 12,000 | – | – | 13,500 | 13,500 | – | – | 20,000 | 20,000 |
| Total for Antibiotics | 110,000 | 650,000 | 12,000 | 12,000 | 123,800 | 732,000 | 13,500 | 13,500 | 187,000 | 1,108,000 | 20,000 | 20,000 |
| Rounded to: | 110,000 | 650,000 | 12,000 | 12,000 | 124,000 | 730,000 | 14,000 | 14,000 | 190,000 | 1,100,000 | 20,000 | 20,000 |
| **Botanicals (Plant Alkaloids, 2,000 Metric Tons/Yr Plant Material)** | | | | | | | | | | | | |
| Wet Plant Material | 2,000 | 4,000 | – | – | 2,250 | 4,500 | – | – | 3,400 | 6,800 | – | – |
| Aqueous Solvent Concentrate | – | – | 720 | 850 | – | – | 810 | 960 | – | – | 1,200 | 1,400 |
| Halogenated Solvent | – | – | 60 | 60 | – | – | 70 | 70 | – | – | 100 | 100 |
| Non-Halogenated Solvent | – | – | 120 | 120 | – | – | 140 | 140 | – | – | 200 | 200 |
| Total for Plant Alkaloids | 2,000 | 4,000 | 900 | 1,030 | 2,250 | 4,500 | 1,020 | 1,170 | 3,400 | 6,800 | 1,400 | 1,700 |
| **Botanicals (Plant Steroids, 150 Metric Tons/Yr Stigmasterol)** | | | | | | | | | | | | |
| Fused Plant Steroid Ingots | 750 | 750 | – | – | 840 | 840 | – | – | 1,000 | 1,000 | – | – |

## TABLE 3.2.1.4.3A (Continued)

| Industry Segment | 1973 | | | | 1977 | | | | 1983 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | | Non-Hazardous | | Hazardous | |
| | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† | Dry Basis | Wet Basis† |
| **Medicinals from Animal Glands (8,000 Metric Tons Glands/Yr)** | | | | | | | | | | | | |
| Extracted Animal Tissue | 7,500 | 7,500 | – | – | 8,400 | 8,400 | – | – | 12,500 | 12,500 | – | – |
| Fats or Oils | 350 | 350 | – | – | 400 | 400 | – | – | 600 | 600 | – | – |
| Filter Cake (Containing protein) | 250 | 500 | – | – | 280 | 560 | – | – | 420 | 840 | – | – |
| Aqueous Solvent Concentrate | – | – | 800 | 1,600 | – | – | 900 | 1,800 | – | – | 1,350 | 2,700 |
| Total Medicinals from Animal Glands | 8,100 | 8,350 | 800 | 1,600 | 9,080 | 9,360 | 900 | 1,800 | 13,520 | 13,940 | 1,350 | 2,700 |
| Total for Production of Active Ingredients (SIC Code 2833) | 172,000 | 1,143,000 | 59,000 | 62,000 | 193,000 | 1,285,000 | 67,000 | 70,000 | 294,000 | 1,937,000 | 99,000 | 103,000 |
| **SIC Code 2831: Biological Products** | | | | | | | | | | | | |
| Aqueous Ethanol Waste from Blood Fractionation | – | – | 250 | 600 | – | – | 280 | 680 | – | – | 400 | 1,000 |
| Antiviral Vaccine | – | – | 300 | 300 | – | – | 350 | 350 | – | – | 500 | 500 |
| Other Biologicals | – | – | 200 | 200 | – | – | 225 | 225 | – | – | 350 | 350 |
| Total for Biological Products | – | – | 750 | 1,100 | – | – | 855 | 1,255 | – | – | 1,250 | 1,850 |
| **SIC Code 2834: Pharmaceutical Preparations** | | | | | | | | | | | | |
| Returned Goods | 10,000 | 10,000 | – | – | 11,300 | 11,300 | – | – | 17,000 | 17,000 | – | – |
| Contaminated or Decomposed Active Ingredient | – | – | 500 | 500 | – | – | 600 | 600 | – | – | 900 | 900 |
| | 10,000 | 10,000 | 500 | 500 | 11,300 | 11,300 | 600 | 600 | 17,000 | 17,000 | 900 | 900 |
| Totals for All Industry Segments | 181,850 | 1,153,000 | 61,650 | 65,100 | 204,300 | 1,836,300 | 70,445 | 73,755 | 311,000 | 1,954,000 | 103,850 | 108,450 |
| Rounded to | 182,000 | 1,153,000 | 62,000 | 65,000 | 204,000 | 1,836,000 | 70,000 | 74,000 | 310,000 | 1,954,000 | 104,000 | 108,000 |

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*Source: Arthur D. Little, Inc., estimates.

†Wet weight estimates are given for all wastes. The two wastes that typically have the highest moisture content are biological sludge and mycelium from fermentations. Where the wet waste estimates are the same as on the dry basis, the waste is usually disposed of with only a minor amount of moisture. However, disposal practices vary from plant to plant, depending on the form in which the waste is produced.

## TABLE 3.2.1.4.3B

## PROJECTED DISTRIBUTION BY STATE OF WASTES GENERATED BY THE PHARMACEUTICAL INDUSTRY IN 1977

(annual metric tons – dry basis)

| | | Hazardous | | | | | | | Non-Hazardous | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | State | Halogenated[1] Solvent Waste | Non Halogenated Solvent Waste | Organic[2] (Chemical) Residues | Contaminated[3] High Inerts Waste | Active Ingredient | Heavy Metals | Total Hazardous* | Biological[4] Sludge | Plant Material[5] Animal Tissue, Fats, Oil | High Inerts[3,6] Waste (Non-Haz.) | Returned Goods | Mycelium[7] | Total Non-Hazardous** |
| IV | Alabama | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Alaska | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IX | Arizona | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Arkansas | – | – | – | – | – | – | – | 100 | – | 10 | 80 | – | 190 |
| IX | California | 370 | 1,800 | 480 | 110 | 45 | – | 2,805 | 3,300 | 370 | 170 | 1,010 | – | 4,850 |
| VIII | Colorado | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Connecticut | 220 | 1,600 | 560 | 110 | 20 | – | 2,510 | 3,400 | 450 | 110 | 340 | – | 4,300 |
| III | Delaware | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Florida | 45 | 450 | 280 | 30 | 6 | – | 811 | 560 | 110 | 35 | 110 | – | 815 |
| IV | Georgia | 70 | 560 | 220 | 30 | 6 | – | 886 | 560 | 110 | 35 | 110 | – | 815 |
| IX | Hawaii | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Idaho | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Illinois | 340 | 3,300 | 860 | 80 | 35 | – | 4,615 | 7,900 | 560 | 200 | 680 | – | 9,340 |
| V | Indiana | 370 | 3,500 | 910 | 80 | 35 | – | 4,895 | 8,600 | 630 | 210 | 730 | – | 10,170 |
| VII | Iowa | 35 | 150 | 55 | 20 | 6 | – | 266 | 790 | 120 | 55 | 110 | – | 1,075 |
| VII | Kansas | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Kentucky | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Louisiana | 10 | 10 | 6 | – | – | – | 26 | 45 | – | 10 | 35 | – | 90 |
| I | Maine | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Maryland | – | – | – | – | – | – | – | 680 | 80 | 20 | 90 | – | 870 |
| I | Massachusetts | – | – | – | – | – | – | – | 680 | 110 | 110 | 110 | – | 1,010 |
| V | Michigan | 220 | 2,100 | 510 | 45 | 20 | – | 2,895 | 5,200 | 380 | 130 | 450 | – | 6,160 |
| V | Minnesota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Mississippi | – | – | – | – | – | – | – | 900 | 220 | 55 | 220 | – | 1,395 |
| VII | Missouri | 120 | 490 | 190 | 80 | 20 | – | 900 | 790 | 80 | 40 | 340 | – | 1,250 |
| VIII | Montana | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VII | Nebraska | 20 | 90 | 35 | 10 | – | – | 155 | – | 40 | 20 | 110 | – | 170 |
| IX | Nevada | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | New Hampshire | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New Jersey | 1,800 | 12,400 | 5,300 | 560 | 130 | – | 20,190 | 27,200 | 3,600 | 1,300 | 2,700 | – | 34,800 |
| VI | New Mexico | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New York | 900 | 6,760 | 2,600 | 340 | 70 | – | 10,670 | 13,500 | 1,800 | 680 | 1,350 | – | 17,330 |
| IV | North Carolina | 110 | 1,000 | 620 | 55 | 20 | – | 1,805 | 1,700 | 340 | 130 | 340 | – | 2,510 |
| VIII | North Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Ohio | 80 | 680 | 170 | 10 | 10 | – | 950 | 1,700 | 120 | 45 | 130 | – | 1,995 |
| VI | Oklahoma | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Oregon | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Pennsylvania | 300 | 3,700 | 1,400 | 150 | 55 | – | 5,605 | 7,300 | 900 | 280 | 960 | – | 9,440 |
| II | Puerto Rico | 220 | 2,200 | 840 | 110 | 20 | – | 3,390 | 4,300 | 560 | 220 | 450 | – | 5,530 |
| I | Rhode Island | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | South Carolina | – | – | – | – | – | – | – | 560 | 110 | 20 | 110 | – | 800 |
| VIII | South Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Tennessee | 110 | 900 | 510 | 55 | 20 | – | 1,595 | 1,100 | 220 | 90 | 220 | – | 1,630 |
| VI | Texas | 110 | 160 | 50 | – | 15 | – | 335 | 300 | – | 35 | 220 | – | 555 |
| VIII | Utah | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Vermont | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Virginia | 45 | 620 | 220 | 20 | 10 | – | 915 | 1,200 | 110 | 55 | 160 | – | 1,525 |
| X | Washington | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | West Virginia | – | – | – | – | – | – | – | 220 | 35 | 10 | 35 | – | 300 |
| V | Wisconsin | 35 | 220 | 55 | 10 | – | – | 320 | 450 | 55 | 10 | 35 | – | 550 |
| VIII | Wyoming | – | – | – | – | – | – | – | – | – | – | – | – | – |
| National Totals | | 5,530 | 42,890 | 15,871 | 1,905 | 543 | 3,280 | 66,539 | 93,035 | 11,110 | 4,085 | 11,225 | 84,000 | 119,455 |
| Region Totals | | | | | | | | | | | | | | |
| | I | 220 | 1,600 | 560 | 110 | 20 | – | 2,510 | 4,080 | 560 | 220 | 450 | – | 5,310 |
| | II | 2,920 | 21,360 | 8,740 | 1,010 | 220 | – | 34,250 | 45,000 | 5,960 | 2,230 | 4,500 | – | 57,660 |
| | III | 345 | 4,320 | 1,620 | 170 | 65 | – | 6,520 | 9,400 | 1,125 | 385 | 1,245 | – | 12,135 |
| | IV | 335 | 2,910 | 1,630 | 170 | 52 | – | 5,097 | 5,380 | 1,110 | 385 | 1,110 | – | 7,965 |
| | V | 1,045 | 9,800 | 2,505 | 225 | 100 | – | 13,675 | 23,850 | 1,745 | 595 | 2,025 | – | 28,215 |
| | VI | 120 | 170 | 56 | – | 15 | – | 361 | 445 | – | 55 | 335 | – | 835 |
| | VII | 175 | 730 | 280 | 110 | 26 | – | 1,321 | 1,580 | 240 | 115 | 560 | – | 2,495 |
| | VIII | – | – | – | – | – | – | – | – | – | – | – | – | – |
| | IX | 370 | 1,800 | 480 | 110 | 45 | – | 2,805 | 3,300 | 370 | 170 | 1,010 | – | 4,850 |
| | X | – | – | – | – | – | – | – | – | – | – | – | – | – |

Notes:
1. Includes R&D solvent waste.
2. Includes biological product organic wastes.
3. Wet weight = dry weight x 2.
4. Wet weight = dry weight x 10.
5. Wet weight = dry weight x 1.2.
6. Includes filter cake from animal source pharmaceuticals.
7. Wet weight = dry weight x 4.35.

*(excludes metals)

**(excludes mycelium)

## TABLE 3.2.1.4.3C

## PROJECTED DISTRIBUTION BY STATE OF WASTES GENERATED BY THE PHARMACEUTICAL INDUSTRY IN 1983

(annual metric tons – dry basis)

| | | Hazardous | | | | | | | Non-Hazardous | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | State | Halogenated[1] Solvent Waste | Non-Halogenated Solvent Waste | Organic[2] (Chemical) Residues | Contaminated[3] High Inerts Waste | Active Ingredient | Heavy Metals | Total Hazardous* | Biological[4] Sludge | Plant Material[5] Animal Tissue, Fats, Oil | High Inerts[3,6] Waste (Non-Haz.) | Returned Goods | Mycelium[7] | Total Non-Hazardous** |
| IV | Alabama | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Alaska | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IX | Arizona | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Arkansas | – | – | – | – | – | – | – | 150 | – | 15 | 120 | – | 285 |
| IX | California | 560 | 2,700 | 730 | 170 | 70 | – | 4,230 | 4,900 | 560 | 250 | 1,500 | – | 7,210 |
| VIII | Colorado | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Connecticut | 340 | 2,400 | 840 | 170 | 30 | – | 3,780 | 5,100 | 680 | 170 | 510 | | 6,460 |
| III | Delaware | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Florida | 70 | 680 | 420 | 40 | 10 | – | 1,220 | 840 | 170 | 50 | 170 | – | 1,230 |
| IV | Georgia | 100 | 840 | 340 | 40 | 10 | – | 1,330 | 840 | 170 | 50 | 170 | – | 1,230 |
| IX | Hawaii | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Idaho | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Illinois | 510 | 4,900 | 1,300 | 120 | 50 | – | 6,880 | 11,800 | 840 | 300 | 1,000 | – | 13,940 |
| V | Indiana | 560 | 5,200 | 1,400 | 120 | 50 | – | 7,330 | 12,800 | 960 | 320 | 1,100 | – | 15,170 |
| VII | Iowa | 50 | 220 | 85 | 30 | 10 | – | 385 | 1,200 | 190 | 85 | 170 | – | 1,645 |
| VII | Kansas | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Kentucky | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VI | Louisiana | 15 | 15 | 10 | – | – | – | 40 | 70 | – | 15 | 50 | – | 135 |
| I | Maine | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Maryland | – | – | – | – | – | – | – | 1,000 | 120 | 30 | 130 | – | 1,280 |
| I | Massachusetts | – | – | – | – | – | – | – | 1,000 | 170 | 170 | 170 | – | 1,510 |
| V | Michigan | 340 | 3,200 | 760 | 70 | 30 | – | 4,400 | 7,800 | 570 | 200 | 680 | – | 9,250 |
| V | Minnesota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Mississippi | – | – | – | – | – | – | – | 1,300 | 340 | 85 | 340 | – | 2,065 |
| VII | Missouri | 190 | 740 | 290 | 120 | 30 | – | 1,370 | 1,200 | 120 | 60 | 510 | – | 1,890 |
| VIII | Montana | – | – | – | – | – | – | – | – | – | – | – | – | – |
| VII | Nebraska | 30 | 130 | 50 | 15 | – | – | 225 | – | 60 | 30 | 170 | – | 260 |
| IX | Nevada | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | New Hampshire | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New Jersey | 2,700 | 18,600 | 7,900 | 840 | 200 | – | 30,240 | 40,800 | 5,400 | 1,800 | 4,000 | – | 53,200 |
| VI | New Mexico | – | – | – | – | – | – | – | – | – | – | – | – | – |
| II | New York | 1,300 | 10,100 | 3,900 | 510 | 100 | – | 15,910 | 20,300 | 2,700 | 1,000 | 2,000 | – | 26,000 |
| IV | North Carolina | 170 | 1,500 | 930 | 85 | 30 | – | 2,715 | 2,500 | 510 | 200 | 510 | – | 3,720 |
| VIII | North Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| V | Ohio | 120 | 1,000 | 250 | 15 | 15 | – | 1,400 | 2,500 | 190 | 70 | 200 | – | 2,960 |
| VI | Oklahoma | – | – | – | – | – | – | – | – | – | – | – | – | – |
| X | Oregon | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Pennsylvania | 460 | 5,600 | 2,100 | 230 | 80 | – | 8,480 | 11,000 | 1,300 | 420 | 1,400 | – | 14,120 |
| II | Puerto Rico | 340 | 3,400 | 1,300 | 170 | 30 | – | 5,240 | 6,400 | 840 | 340 | 680 | – | 8,260 |
| I | Rhode Island | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | South Carolina | – | – | – | – | – | – | – | 840 | 170 | 30 | 170 | – | 1,210 |
| VIII | South Dakota | – | – | – | – | – | – | – | – | – | – | – | – | – |
| IV | Tennessee | 170 | 1,200 | 780 | 90 | 30 | – | 2,346 | 1,700 | 340 | 130 | 340 | – | 2,510 |
| VI | Texas | 170 | 240 | 80 | – | 25 | – | 515 | 460 | – | 50 | 340 | – | 850 |
| VIII | Utah | – | – | – | – | – | – | – | – | – | – | – | – | – |
| I | Vermont | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | Virginia | 70 | 930 | 340 | 30 | 15 | – | 1,385 | 1,900 | 170 | 85 | 240 | – | 2,395 |
| X | Washington | – | – | – | – | – | – | – | – | – | – | – | – | – |
| III | West Virginia | – | – | – | – | – | – | – | 340 | 50 | 15 | 50 | – | 455 |
| V | Wisconsin | 50 | 340 | 85 | 15 | – | – | 490 | 680 | 85 | 15 | 50 | – | 830 |
| VIII | Wyoming | – | – | – | – | – | – | – | – | – | – | – | – | – |
| National Totals | | 8,315 | 64,035 | 23,870 | 2,985 | 815 | 4,800 | 99,890 | 139,520 | 16,895 | 6,085 | 16,770 | 127,000 | 178,070 |
| Regional Totals | | | | | | | | | | | | | | |
| | I | 340 | 2,400 | 840 | 170 | 30 | – | 3,780 | 6,100 | 850 | 340 | 680 | – | 7,970 |
| | II | 4,340 | 32,100 | 13,100 | 1,520 | 330 | – | 51,390 | 67,600 | 8,940 | 3,240 | 6,680 | – | 88,460 |
| | III | 530 | 6,530 | 2,440 | 250 | 95 | – | 9,845 | 14,240 | 1,640 | 550 | 1,820 | – | 18,250 |
| | IV | 510 | 4,220 | 2,460 | 250 | 80 | – | 7,610 | 8,020 | 1,700 | 545 | 1,700 | – | 11,965 |
| | V | 1,580 | 14,640 | 3,785 | 340 | 145 | – | 20,500 | 35,580 | 2,636 | 905 | 3,030 | – | 42,150 |
| | VI | 185 | 255 | 90 | – | 25 | – | 555 | 680 | – | 80 | 510 | – | 1,270 |
| | VII | 270 | 1,090 | 425 | 165 | 40 | – | 1,980 | 2,400 | 370 | 175 | 850 | – | 3,795 |
| | VIII | – | – | – | – | – | – | – | – | – | – | – | – | – |
| | IX | 560 | 2,700 | 730 | 170 | 70 | – | 4,230 | 4,900 | 560 | 250 | 1,500 | – | 7,210 |
| | X | – | – | – | – | – | – | – | – | – | – | – | – | – |

Notes:
1. Includes R&D solvent wastes.
2. Includes biological product organic wastes.
3. Wet weight = dry weight x 2.
4. Wet weight = dry weight x 10.
5. Wet weight = dry weight x 1.2.
6. Includes filter cake from animal source pharmaceuticals.
7. Wet weight = dry weight x 4.35.

*(excludes metals)
**(excludes mycelium)

## DATA SOURCES FOR SECTION 3.1

### A. GENERAL SOURCES

Manufacturers' Technical Bulletins – This is usually the best single source of general information about the compound.

Material Safety Data Sheets – Provided by the manufacturer using the U.S. Department of Labor Form OSHA-20 or an approved modification.

Code of Federal Regulations – Office of the Federal Register, Archives and Record Service, Washington, D.C., 1972. Titles 46 (Shipping) and 49 (Transportation) in the most recent revision available.

Chemical Safety Data Sheets – Manufacturing Chemists Association, Washington, D.C.

Industrial Safety Data Sheets – National Safety Council, Chicago, Illinois.

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Petroleum Products Handbook – V.B. Guthrie (ed.), McGraw-Hill, New York, 1960.

Glossary of Terms Used in Petroleum Refining – 2nd edition, American Petroleum Institute, New York, 1962.

The Handling and Storage of Liquid Propellants – Office of Defense Research and Engineering, U.S. Government Printing Office, Washington, D.C., 1963.

Industrial Chemicals – W.L. Faith, D.B. Keyes, and R.L. Clark, 3rd edition, Wiley, New York, 1965.

Chemical Technology of Petroleum – W.A. Gruse and D.R. Stevens, 3rd edition, McGraw-Hill, New York, 1960.

Chemical Rocket/Propellant Hazards – CPIA Publication No. 194, Vol. III, 1970.

Organic Solvents – J.A. Riddick and W.B. Bunger, 3rd edition, Wiley-Interscience, New York, 1970.

Transport of Dangerous Goods – (4 vols) United Nations, New York, 1970.

Kirk-Othmer Encyclopedia of Chemical Technology – 1st edition (1947-1960) and 2nd edition (1963-1970), Interscience-Wiley, New York.

Evaluation of the Hazard of Bulk Water Transportation of Industrial Chemicals, A Tentative Guide – National Academy of Sciences, Washington, D.C., 1970; includes supplement with additions to September 1972.

System for Evaluation of the Hazards of Bulk Water Transportation of Industrial Chemicals – National Academy of Sciences, Washington, D.C., 1974.

## B. HEALTH HAZARDS

Industrial Hygiene and Toxicology – F.A. Patty, 2nd edition, Vol. II, Interscience, New York, 1963.

Toxicity and Metabolism of Industrial Solvents – E. Browning, Elsevier, New York, 1965.

Practical Toxicology of Plastics – R. Lefaux, CRC Press, Cleveland, Ohio, 1968.

Industrial Toxicology – L.T. Fairhill, Williams and Wilkins, 2nd edition, Baltimore, Maryland, 1957.

Toxicology of Drugs and Chemicals – W.B. Deichmann and H.W. Girarde, Academic Press, New York, 1969.

Clinical Toxicology of Commercial Products – M.N. Gleason, et al., 3rd edition, Williams and Wilkins, Baltimore, Maryland, 1969.

Handbook of Toxicology: Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals – W.S. Spector, Saunders, Philadelphia, Pa., 1956.

Occupational Diseases: A Guide to Their Recognition – U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1097. Superintendent of Documents, Washington, D.C., 1964.

First Aid Textbook – American National Red Cross, Washington, D.C., 1972.

Electrical Safety Practice: Odor Warning for Safety – Monograph 113 Instrument Society of America (ISA), Pittsburgh, Pa., 1972.

Toxic Substances – Annual List 1973 – H.E. Christensen, U.S. Department of Health, Education, and Welfare, Superintendent of Documents, Washington, D.C., 1973.

Encyclopedia of Occupational Health and Safety, Two Volumes, International Labour Organization, Geneva, 1972.

Fawcett, H.H., Toxicity vs. Hazard, pages 279-289, and Foulger, J.H., Effect of Toxic Agents, pages 250-278, in Fawcett and Wood, Safety and Accident Prevention in Chemical Operations, Interscience, Wiley, New York, 1965.

Murphy, Sheldon C., The Toxicity of Pesticides and Their Metabolites, pages 313-335, in Degradation of Synthetic Organic Molecules in the Biosphere – Natural, Pesticidal, and Various Other Man-Made Compounds, Proceedings of a Conference, San Francisco, California, June 12-13, 1971, Committee on Agriculture and the Environment, ISBN 0-309-02046-8, National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, D.C. 20418, 1972.

## C. FIRE HAZARDS

The Fire and Explosion Hazards of Commercial Oils – W. Vlachos and C.A. Vlachos, Vlachos and Co., Philadelphia, Pa., 1921.

1972 Annual Book of ASTM Standards – American Society for Testing and Materials, Philadelphia, Pa., 1972.

Fire Protection Guide on Hazardous Materials – 5th edition, Nos. 325A, 325M, 49, 491M, and 704M, National Fire Protection Association (NFPA), Boston, Mass., 1972.

Fire Protection Handbook – G.H. Tryon (ed.), 13th edition, National Fire Protection Association (NFPA), Boston, Mass., 1969.

Handbook of Industrial Loss Prevention – 2nd edition, Factory Mutual Engineering Corp., McGraw-Hill, New York, 1967.

## D. WATER POLLUTION

Water Quality Criteria Data Book – Vol. 1 – Organic Chemicals (1970) and Vol. 2 – Inorganic Chemicals (1971), Vol. 5 – Effect of Chemicals on Aquatic Life (1974), United States Environmental Protection Agency, Superintendent of Documents, Washington, D.C.

Engineering Management of Water Quality – P.H. McGauhey, McGraw-Hill, New York, 1968.

The BOD of Textile Chemicals – Proceedings of the American Association of Textile Chemists and Colorists, *American Dyestuff Reporter,* August 29, 1966, p. 39.

Biodegradable Surfactants for the Textile Industry – *American Dyestuff Reporter,* January 30, 1967.

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# 4.0 TREATMENT AND DISPOSAL TECHNOLOGIES

## 4.1 BACKGROUND

Approximately 244,000 metric tons of land-destined process wastes (dry weight basis) are generated annually by the pharmaceutical industry.* The amount of hazardous wastes generated is about 25 percent of the total waste, or 61,000 metric tons per year. The waste generation rate is expected to grow to nearly 400,000 metric tons of total wastes per year and to 100,000 metric tons of hazardous wastes per year by 1983.

## 4.2 DESCRIPTION OF PRESENT TREATMENT AND DISPOSAL TECHNOLOGIES

Approximately 85 percent of current total wastes generated and 60 percent of current hazardous wastes generated are estimated to be both treated and then disposed of by contractors. Of the current total wastes generated, ADL estimates that 60 percent, or 150,000 metric tons, are disposed of on land. About 9 percent, or 5600 metric tons, of current hazardous wastes generated are disposed of on land. These percentages reflect the extensive use of incineration by the pharmaceutical industry both on-site and by contractors off-site. Where possible, materials are recovered for reuse. Secure chemical landfills and encapsulation techniques are now being used – and will most probably be in the future – for the disposal of heavy metal wastes which are too dilute or contaminated for recovery, and general process wastes of a non-hazardous nature.

The current process waste treatment and disposal methods are briefly described in Section 4.2.1; for each hazardous waste identified in Chapter 3, current treatment and disposal practices are discussed in Sections 4.2.2 to 4.2.6. Section 4.2.7 describes the treatment and disposal methods discussed in the sections on hazardous waste treatment and disposal.

### 4.2.1 Present Treatment/Disposal Technologies for General Process Wastes (Hazardous and Non-hazardous)

#### *4.2.1.1 Research and Development*

Numerous large pharmaceutical companies have research and development operations. In fact, there are currently 25,000 researchers within the industry.

The wastes from this industry section include:

- waste solvents and still bottoms, and
- test animals.

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*See Table 3.2.1.4 for summary of total process wastes and potentially hazardous wastes for the pharmaceutical industry in 1973.

Waste solvents and still bottoms (1500 metric tons annually) are either disposed of by contract incineration, or are company-incinerated, if the research facility is located near pharmaceutical manufacturing operations with liquid incineration capability.

Test animals are either rendered or incinerated. Large animals are rendered with the bones converted to bonemeal. Small animals are usually incinerated and the inert ash is sent to a landfill. Often these small animals are either autoclaved or frozen, if the animals are not to be incinerated immediately.

#### *4.2.1.2 Production of Active Ingredients (SIC 2831 and 2833)*

##### 4.2.1.2.1 Organic Medicinal Chemicals

Pharmaceutical companies manufactured about 75 million pounds of organic medicinal chemicals in 1973.* The wastes from these operations include:

- waste solvents, halogenated and non-halogenated;
- organic chemical residues;
- biological sludge (from organic chemical wastewater treatment);
- heavy metals, and
- high inert content wastes such as filter cakes.

With the exception of the biological sludge and part of the high inert content wastes, they are all hazardous wastes. The present methods of hazardous waste treatment and disposal are discussed in more detail in Sections 4.2.2 through 4.2.6.

The pharmaceutical industry recovers a large amount (95 percent or more) of its process solvents for reuse. Those solvents that are considered wastes come from solvent-recovery operations. Essentially all of these waste solvents are incinerated, either on-site or by contractors off-site. Organic chemical residues are usually incinerated, although some operations are sending them to landfills off-site.

ADL surveyed about 25 to 30 percent of the pharmaceutical companies' production capacity of organic chemicals for this study. Of those visited, half had on-site biological treatment of waste water; 90 percent disposed of the resulting sludge in off-site landfills.

Heavy metals are used as catalysts, oxidants, and product ingredients in the production of organic medicinal chemicals. A limited amount is used within the pharmaceutical industry (see Section 3.2.1.2.1). The locations using heavy metals are also limited. The heavy metal wastes are handled in various ways, including recovery off-site and encapsulation and landfill in a separate section of a landfill. These methods are discussed further in Section 4.2.5.

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*See Section 3.2.1.2.

The properties of the high inert content wastes vary greatly. ADL estimates that as much as 30 percent of those materials are potentially hazardous because of flammability, corrosiveness, or toxicity. The remaining 70 percent are innocuous materials, such as filter aid and water or charcoal and water, which are usually landfilled. Of the 30 percent that are potentially hazardous some are considered potentially hazardous from the standpoint of flammability because of the presence of solvent. These can be rendered non-hazardous by incineration. About 25 companies incinerate this material. The remainder of the potentially hazardous waste must be landfilled with special precautions because they contain material such as heavy metals. These cannot be incinerated.

#### 4.2.1.2.2 Inorganic Medicinal Chemicals

Since most inorganic medicinal-chemical active ingredients are purchased from sources outside the pharmaceutical industry, there is little waste produced in this industry section. Preparations such as stomach antacids are, however, generally produced within the pharmaceutical industry. While the majority of the process waste leaves with the water effluent, there may infrequently be reject materials, such as aluminum hydroxide or magnesium hydroxide. These wastes may be landfilled.

The only hazardous waste stream we found in this industry segment was a waste which contained about 0.2 percent selenium. The waste, about 160,000 kg per year, is in its most insoluble form, the sulfide, when it is disposed of by a contractor in a state-approved secure chemical landfill.

#### 4.2.1.2.3 Fermentation Products

When active ingredients such as antibiotics are produced by fermentation, three types of wastes that are destined for land disposal are also produced.* They are:

- Mycelia;
- Biological sludge from spent broth treatment;
- Solvent concentrate (hazardous waste, see section 3.2.1.2.3).

Because there are few companies involved in fermentation and most of the operations are large scale, ADL was able to study about 65 percent of the U.S. fermentation production capacity. The volumes of waste from such operations represent a significant problem to the industry.

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* Figure 3.2.1.2.3 shows the waste generation from a typical fermentation product – penicillin.

Of the estimated 75,000 metric tons of mycelia (on a dry basis) produced by fermentation operations each year, ADL estimates that 85 to 90 percent of the waste is land-disposed at some off-site location. Of the remainder, some portions are incinerated or used as soil builders. In the past, ocean dumping was used for mycelia disposal, until 1972 EPA regulations on ocean dumping halted this practice temporarily by invoking stricter requirements on analysis of wastes prior to permit renewals. A typical large operation has on the order of 25,000 to 45,000 metric tons of mycelia to dispose of each year. Since this material is wet (generally 25 to 35 percent solids after dewatering), it must be disposed of immediately to eliminate odor problems.

Many disposal methods have been investigated. When mixed with 1 percent lime, for example, mycelia can be used as a soil builder. It can also be incinerated, but the water content is too high for the operation to be cost-effective. Although this waste is not considered hazardous, it is indeed a problem for the industry.

Waste broth solids are high-volume materials which can either be disposed of as a waste or can be changed to a useful by-product. About 72,000 metric tons are produced annually by fermentation operations. Until stricter effluent restrictions were placed on fermentation operations, the spent broth was usually treated biologically, producing a sludge that was landfilled. Approximately 0.5 kg of biological sludge is produced for each kg of waste broth solids. Since the spent broth contains a significant amount of food value, it can be concentrated by evaporation and sold as a molasses substitute in animal feeds. Still some operations handle the broth as a waste either because the capital investment for the equipment is too great, or because there is no market for the concentrate. None of those operations producing the broth concentrate are making a profit, just breaking even at best. On the other hand, they do not have the significant cost of biologically treating the high BOD waste. Occasionally the waste broth is incinerated, even though incineration is expensive because of the relatively low-Btu content of the waste broth.

The third type of waste, the solvent concentrate, which is a waste product of solvent recovery operations, contains as much as 50 percent by weight of organic solids. About 50 million pounds of the concentrate is produced annually by fermentation operations within the United States. Sixty-five percent of the pharmaceutical industry fermentation production capacity was surveyed. The waste solvent concentrate at all these locations was incinerated either on-site or by contractors off-site. Because of the similar nature of the other plants in this industry, we estimate that all of this waste is currently being incinerated, either on-site or by contractors off-site. Because this waste is flammable, it is considered hazardous. Disposal is discussed further in Section 4.2.2.2.3.

#### 4.2.1.2.4 Botanicals

Medicinal active ingredients, such as alkaloids and steroids, are obtained from plant material. The wastes potentially destined for land disposal are listed below, the last two being hazardous:

- Moisture-laden plant material,
- Waste solvent (50 percent solids and 30 percent water), and
- Waste chlorinated hydrocarbons.

A typical alkaloid operation* produces 1820 kg per day of wet waste plant material and operates 250 days per year. This totals to 454 metric tons per year of waste plant material. The waste is steamed to remove residual solvent and is then sent to sanitary landfill off-site.

Three types of solvents are used in the extraction process to produce alkaloids. The one used in the initial extract ends up with water, plant extract, and organic acid salts after solvent-recovery operations. This waste solvent is either incinerated on-site or by contractors off-site. A second water-immiscible, chlorinated solvent, is used to extract the alkaloid from the first solvent. More of the chlorinated solvent can be recovered than the first solvent which contains most of the water-soluble organic material after extraction. But, since this second solvent is chlorinated, problems can develop if it is incinerated without the proper precautions. The amount of chlorinated solvent is only 5 cubic meters (1,250 gallons) per year for the typical plant, five percent of the total solvent. This amount is small enough to drum for contractor incineration. We estimate that 60 percent of each of the two waste solvents are incinerated on-site and the remainder off-site by contractors. A third waste solvent is non-halogenated.

#### 4.2.1.2.5 Drugs from Animal Sources

Medicinal products such as insulin or heparin are obtained from animal sources. The wastes from these operations that are destined for land disposal include:

- rendered organs or animal tissue;
- fats and oils;
- filter cake, containing precipitated protein; and
- aqueous solvent (hazardous waste, see Section 3.2.1.2.5).

The typical extraction operation** will dispose of 839 metric tons of organs or animal tissue annually in the production of 284 kg of active ingredient. Two methods of disposal are used interchangeably in most operations. When a market exists, the waste product is sold as a protein-source feed for animals; otherwise it is disposed of in a sanitary landfill. The fats (40 metric tons per year) are recovered for sale to soap manufacturers. The filter cake (25.5 metric tons per year), which contains precipitated protein, is landfilled or incinerated if the operation is near other pharmaceutical operations with incineration capability.

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* Figure 3.2.1.2.4.1 presents the flow scheme of waste generation for a typical alkaloid operation.

** Figure 3.2.1.2.5 describes the waste generation in a typical operation extracting glandular materials.

The hazardous waste from the operation in which medicinals are obtained from animal glands is a waste solvent emanating from the solvent-recovery system. A typical operation produces 91 metric tons (25,000 gallons) of waste solvent annually, a generation rate of 350 liters per kilogram of product. These solvents, which contain 50 percent water and 25 percent organic solids, are incinerated either on-site or by a contractor off-site.

#### 4.2.1.2.6 Biological Products

Some pharmaceutical companies manufacture biological products such as blood products, vaccines, serums and toxoids. The wastes from these operations include:

- Aqueous solvent waste;
- Miscellaneous incineratable wastes; and
- Filter material.

ADL estimates that SIC 2831 has 500 metric tons of hazardous waste. Most of this amount is considered hazardous because of its flammability. All hazardous wastes are incinerated either on-site or by contractor off-site. The filter material contains only traces of protein and can be landfilled.

### *4.2.1.3 Formulation and Packaging (SIC 2834)*

The wastes from the formulation and packaging segment of the pharmaceutical industry are returned goods and reject material.* The total returned goods and reject material from this segment annually are indicated below:

| | |
|---|---|
| • Glass, paper, water, etc. | 10,000 metric tons |
| • Active ingredient | 500 metric tons |

Normal trash waste from the formulation and packaging segment of the industry is handled in much the same way as in other industries. Paper, cartons, and the like, not identifiable as the company's own can be recycled through salvage dealers, while materials bearing the company's name are either shredded or incinerated on-site.

Returned goods are handled specifically by the formulating and packaging operations of a company. "Controlled drugs," such as narcotics, must be destroyed in the presence of Drug Enforcement Agency (DEA) personnel, according to the regulation which is presented on the next page. Other pharmaceuticals are handled in a method detailed by the specific company and pharmaceuticals recalled by the FDA may be required to be destroyed under FDA observation. Generally, non-salvageable goods are crushed on-site and then sent to landfill. Smaller percentages are either incinerated or are slurried with water which is sent to an activated sludge treatment facility.

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*Section 3.2.1.3 discusses waste generation in this industry segment.

## Federal Regulations: Disposal of Controlled Pharmaceuticals[†]

### § 1307.15 Incidental manufacture of controlled substances.

Any registered manufacturer who, incidentally but necessarily, manufactures a controlled substance as a result of the manufacture of a controlled substance or basic class of controlled substance for which he is registered and has been issued an individual manufacturing quota pursuant to Part 1303 of this chapter (if such substance or class is listed in schedule I or II) shall be exempt from the requirement of registration pursuant to Part 1301 of this chapter and, if such incidentally manufactured substance is listed in schedule I or II, shall be exempt from the requirement of an individual manufacturing quota pursuant to Part 1303 of this chapter, if such substances are disposed of in accordance with § 1307.21.

### DISPOSAL OF CONTROLLED SUBSTANCES

### § 1307.21 Procedure for disposing of controlled substances.

(a) Any person in possession of any controlled substance and desiring or required to dispose of such substance may request the Regional Administrator of the Administration in the region in which the person is located for authority and instructions to dispose of such substance. The request should be made as follows:

(1) If the person is a registrant required to make reports pursuant to Part 1304 of this chapter, he shall list the controlled substance or substances which he desires to dispose of on the "b" subpart of the report normally filed by him, and submit three copies of that subpart to the Regional Administrator of the Administration in his region;

(2) If the person is a registrant not required to make reports pursuant to Part 1304 of this chapter, he shall list the controlled substance or substances which he desires to dispose of on DEA Form 41, and submit three copies of that form to the Regional Administrator in his region; and

(3) If the person is not a registrant, he shall submit to the Regional Administrator a letter stating:

(i) The name and address of the person;

(ii) The name and quantity of each controlled substance to be disposed of;

(iii) How the applicant obtained the substance, if known; and

(iv) The name, address, and registration number, if known, of the person who possessed the controlled substances prior to the applicant, if known.

(b) The Regional Administrator shall authorize and instruct the applicant to dispose of the controlled substance in one of the following manners:

(1) By transfer to person registered under the Act and authorized to possess the substance;

(2) By delivery to an agent of the Administration or to the nearest office of the Administration;

(3) By destruction in the presence of an agent of the Administration or other authorized person; or

(4) By such other means as the Regional Administrator may determine to assure that the substance does not become available to unauthorized persons.

(c) In the event that a registrant is required regularly to dispose of controlled substances, the Regional Administrator may authorize the registrant to dispose of such substances, in accordance with paragraph (b) of this section, without prior approval of the Administration in each instance, on the condition that the registrant keep records of such disposals and file periodic reports with the Regional Administrator summarizing the disposals made by the registrant. In granting such authority, the Regional Administrator may place such conditions as he deems proper on the disposal of controlled substances, including the method of disposal and the frequency and detail of reports.

(d) This section shall not be construed as affecting or altering in any way the disposal of controlled substances through procedures provided in laws and regulations adopted by any State.

[36 F.R. 7801, Apr. 24, 1971, as amended at 37 F.R. 15922, Aug. 8, 1972]

### § 1307.22 Disposal of controlled substances by the Administration.

Any controlled substance delivered to the Administration under § 1307.21 or forfeited pursuant to section 511 of the Act (21 U.S.C. 881) may be delivered to any department, bureau, or other agency of the United States or of any State upon proper application addressed to the Administrator, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20083. The application shall show the name, address, and official title of the person or agency to whom the controlled drugs are to be delivered, including the name and quantity of the substances desired and the purpose for which intended. The delivery of such controlled drugs shall be ordered by the Administrator, if, in his opinion, there exists a medical or scientific need therefor.

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[†] Source: Code of Federal Regulations, No. 21, Food and Drugs, Part 1300 to end.

Reject material from formulation is very limited. Because of the value of the raw materials involved, potentially faulty batches of pharmaceuticals are reformulated to meet specifications. When a material cannot be upgraded, the "bad batches" are either inactivated, by neutralization, for example, and sent through biological treatment, or are landfilled or incinerated, depending upon the nature of the material.

(For the purpose of this study, a portion of the returned goods and reject material have been segregated as potentially hazardous wastes.) Section 4.2.4 provides a more detailed discussion on present treatment and disposal technologies of the potentially hazardous wastes resulting from the returned goods and reject material. Section 4.5.5 describes Level I, II, and III technologies for treating and disposing of returned goods and reject material from formulation.

### *4.2.1.4 Marketing and Distribution*

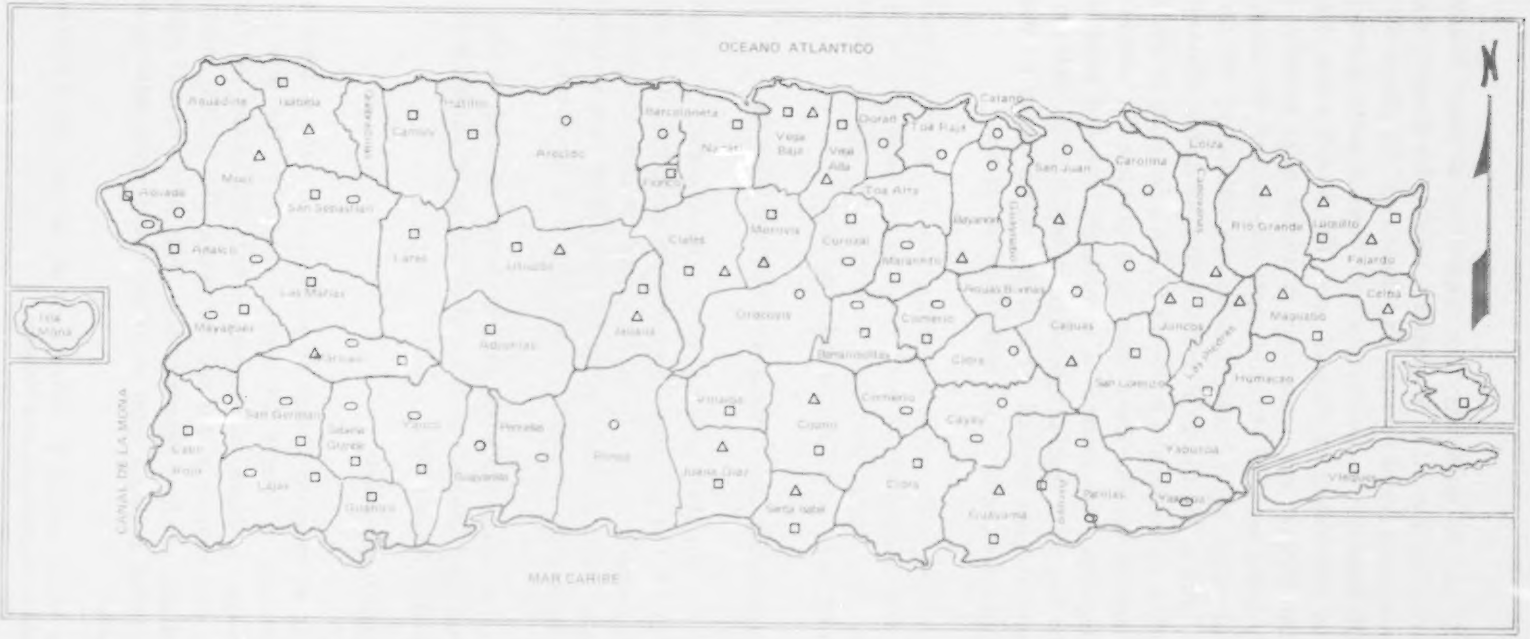
Wastes from marketing and distribution merely represent large volumes of paper, wood, and cardboard. Since there are no process wastes from this segment of the industry and returned goods are normally sent back to the formulation and packaging facilities, this segment of the industry has not been studied further.

### *4.2.1.5 Pharmaceutical Operations in Puerto Rico*

An organization called Fomento was set up by the Puerto Rican government to encourage industry to settle in Puerto Rico and to provide assistance to those companies in the areas of siting, employment, and services, such as electricity, water, and regional wastewater treatment. Industries investigating the attractive tax-break offers in the mid-'60's were also told that, should they settle in an area like Barceloneta (about 40 miles west of San Juan) adequate regional wastewater treatment facilities would be provided. The planned completion date has slipped a little. It was planned to be on stream in 1974, but it will probably not be in operation until mid-1975. Therefore, pharmaceutical companies involved have had to ocean-dump their process wastewater, because they are not permitted to send it to the nearby Manati River.

Numerous U.S. and European pharmaceutical firms were encouraged to construct operations in Puerto Rico. Since the early '60's, the number of these installations has been growing rapidly. At present, we estimate that as many as 42 plants have been constructed and are now in operation. These operations have severe impacts on the pollution control problems of the area.

Solid waste disposal sites are provided by the local municipal governments in Puerto Rico (see Figure 4.2.1.5 for outline of current facilities). In the past these disposal sites have simply been dumps with open burning of trash. The Puerto Rican Environmental Quality Board (EQB) is pressuring the municipalities to upgrade the disposal sites and to provide sanitary landfills. The EQB does not consider two of the sites – the Manati dump and the


OCEANO ATLANTICO
MAR CARIBE
CANAL DE LA MONA
N
Isla Mona
Aguadilla
Isabela
Quebradillas
Camuy
Hatillo
Arecibo
Barceloneta
Manati
Vega Baja
Vega Alta
Dorado
Toa Baja
Cataño
San Juan
Carolina
Loiza
Canovanas
Rio Grande
Luquillo
Fajardo
Ceiba
Rincon
Moca
San Sebastian
Añasco
Las Marias
Mayaguez
Lares
Utuado
Ciales
Morovis
Corozal
Toa Alta
Bayamon
Guaynabo
Naranjito
Aguas Buenas
Caguas
Juncos
Las Piedras
Naguabo
Humacao
Yabucoa
Maunabo
Patillas
Arroyo
Guayama
Cidra
Cayey
Comerio
Barranquitas
Orocovis
Jayuya
Adjuntas
Maricao
San German
Sabana Grande
Yauco
Guanica
Lajas
Cabo Rojo
Guayanilla
Peñuelas
Ponce
Villalba
Juana Diaz
Coamo
Santa Isabel
Salinas
Aibonito
San Lorenzo
Gurabo
Trujillo Alto
Vieques
Culebra

○ Sanitary Landfill

○ Dumps Converted to Sanitary Landfill

⬭ Approved Lands

□ Open Dump with Burning

△ Lands Under Study

†Source: Environmental Quality Board of Puerto Rico.

FIGURE 4.2.1.5 SOLID WASTE DISPOSAL FACILITIES IN PUERTO RICO†

Barceloneta landfill – to be satisfactory for disposal of chemical wastes. But the EQB considers a third site – the landfill at Mayagüez – suitable for chemical wastes. In addition a new site has been recommended between Barceloneta and Arecibo in the Caña Tiburones area which the EQB feels will be satisfactory for chemical waste disposal. We visited the Manati, Barceloneta, and Mayagüez disposal sites. The Manati dump clearly is not satisfactory for chemical disposal and is currently no longer being so used. The Barceloneta landfill is currently being used for chemical waste disposal and, on casual examination, it appears that the site could be upgraded to serve as a satisfactory site for chemical waste disposal. However, studies by the EQB indicate that subsurface drainage to the nearby Manati River would be excessive, and hence the EQB is attempting to stop the municipality from accepting chemical wastes. There may be a problem for several months as the pharmaceutical companies were assured of municipally operated solid waste and liquid waste facilities. The Mayagüez landfill appears to be well located, well run, and should be satisfactory for chemical waste disposal. There is at least one company available to recover and incinerate solvents on a contract basis in the Barceloneta area.

The Commonwealth of Puerto Rico appears presently to be making good progress in improving the handling of solid wastes, but regulations and facilities have lagged behind U.S. mainland practices. An excerpt from a development plan for a proposed Solid Waste Management Authority is presented on the following page.

### 4.2.2 Present Treatment/Disposal Technologies for Waste Solvents

Small companies and R&D installations in isolated areas are currently disposing of some solvents by landfill, but the trend is to incinerate waste solvents. Depending upon local conditions, outside contractors may be used for waste incineration by both large and small companies, or large companies may choose to install their own incinerators. Table 4.2.2 summarizes the disposal methods used for waste solvents in the pharmaceutical industry.

Incineration is an environmentally adequate means of waste solvent disposal.* Where quantities of halogenated solvent are incinerated the use of scrubbing to minimize the air pollution risk should be investigated.

#### *4.2.2.1 Research and Development*

Since there is no measurable unit of production for the research and development operations, the amount of wastes has been estimated on the basis of the number of researchers. Although the degree of recovery is not well known for this segment of the industry, solvents are commonly distilled for reuse. The 25,000 members of the R&D section of the industry produce approximately 1500 metric tons of mixed waste solvents each year. This number is based upon an extrapolation using data supplied to ADL by a number of companies.

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*Tables 4.5.1-A and 4.5.1-B describe the various levels of treatment and disposal technologies used for waste-solvent disposal in the pharmaceutical industry.

## A Plan for Hazardous Waste Disposal in Puerto Rico[†]

**The proposed Authority should have the sole responsibility in Puerto Rico for processing, recovery, disposing, and storing of hazardous and toxic wastes, in order to provide uniform and reliable control. The proposed Authority should serve as a servicing agent for all producers of hazardous and toxic wastes. Sites and handling techniques conforming to Puerto Rico Environmental Quality Board and Federal standards should be established. Special user fees should be charged producers of these wastes, based upon difficulty and expense of providing this service. The service should not only be self-liquidating financially, but produce a replacement fund for facilities and equipment.**

### Program Recommendations

Currently, Federal standards governing hazardous and toxic wastes are still pending, and patterning a program for Puerto Rico according to these standards appears speculative. Nevertheless, enough is now known about types and classes of these wastes to begin forming directions for Puerto Rico. Therefore, the following steps should be taken to initiate an operating capability for handling hazardous and toxic wastes by the proposed Authority.

1. Conduct an island-wide survey to determine the types, amounts, and locations of hazardous and toxic waste production. Identification of present storage sites should be made as well.

2. Investigate and evaluate existing Commonwealth of Puerto Rico and Federal regulations applicable to hazardous and toxic wastes.

3. Develop a plan which can be implemented by the Authority for handling hazardous and toxic wastes in Puerto Rico. The plan should consider such aspects as:

   (a) Land disposal methods
   (b) Disposal facility locations
   (c) Topographical and geological conditions
   (d) Drainage control
   (e) Protection of water supplies
   (f) Handling hazards and protection
   (g) Transportation and unloading
   (h) Security
   (i) Personnel training and safety
   (j) Records and monitoring
   (k) Technologies of processing and storing
   (l) Prevention of accidental catalytic reactions
   (m) Abandonment of sites

4. An adjunct to this plan should be a locational plan showing desirable locations for new industries which may have hazardous and toxic substances as a manufacturing by-product. These locations should be amenable to the environment. Industries producing hazardous and toxic wastes should be prohibited from any location not specified for this purpose. The industrial location plan should be developed and implemented in conjunction with the Environmental Quality Board, Fomento, Department of Natural Resources, the Planning Board, and the Department of Health.

5. All plans developed for hazardous and toxic wastes must comply with regulations of the Environmental Quality Board, the Environmental Protection Agency and other applicable Commonwealth of Puerto Rico standards.

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[†] Source: Proposed Solid Waste Management, Environmental Quality Board, Puerto Rico.

## TABLE 4.2.2

## WASTE SOLVENT DISPOSAL METHODS[†]

| | | Current Disposal Methods | | | |
|---|---|---|---|---|---|
| | | On-Site | | | Off-Site |
| Industry Segment | Total Hazardous Waste (metric tons per year) | Incineration | Incineration At Nearby Company-Owned Facility | Other* | Incineration by Contractor |
| **R&D** | 1,500 | – | 450 | – | 1,050 |
| **Active Ingredient Production** | | | | | |
| Organic Medicinal Chemicals | | | | | |
| Halogenated solvent | 3,400 | 800 | – | – | 2,600 |
| Non-halogenated solvent | 23,800 | 9,300 | | | 14,500 |
| Inorganic Medicinal Chemicals | 0 | – | – | – | – |
| Fermentation products | 12,000 | 5,000 | – | – | 7,000 |
| Botanicals | | | | | |
| Aqueous solvent | 1,000 | 400 | – | – | 600 |
| Halogenated solvent | 50 | 5 | – | – | 45 |
| Non-halogenated solvent | 120 | 50 | – | – | 70 |
| Drugs from Animal Sources | 800 | 260 | – | 40 | 500 |
| Biologicals | 250 | 100 | – | – | 150 |
| **Formulation & Packaging** | 0 | – | – | – | – |
| Total | 42,920 | 15,915 | 450 | 40 | 26,515 |

*Treatment in on-site biological wastewater treatment facility or in municipal system.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

R&D installations surveyed were either sending waste solvents to contractors for incineration off-site (about 70 percent is estimated to be disposed of in this manner), or were incinerating them in nearby company-owned facilities. The Laboratory Waste Disposal Manual published by the Manufacturing Chemists' Association, Inc., suggests incineration for even very small amounts of solvents. Incineration of these waste solvents is an environmentally adequate disposal technique.

### *4.2.2.2 Production of Active Ingredients (SIC 2831 and 2833)*

When the pharmaceutical industry was much smaller, most pharmaceutical companies discarded waste solvents and still bottoms in dumps or landfills. With the increased production of active ingredients, greater difficulty in finding suitable landfills, and more stringent state and local government controls, incineration is being increasingly employed for disposal of waste solvents.

#### 4.2.2.2.1 Organic Medicinal Chemicals

We estimate that all waste solvents from solvent-recovery operations used in the production of organic medicinal chemicals are disposed of by incineration. Approximately half of the larger pharmaceutical companies have some on-site incineration capacity, even though they may send more troublesome wastes, such as halogenated solvents, to off-site contractors. Others continue to utilize outside contractors; however, some additional pharmaceutical companies are currently planning on-site incineration. For this study, ADL surveyed about 25 to 30 percent of the production capacity of organic medicinal chemicals of the pharmaceutical companies. Since the production of active ingredients is centered in the larger pharmaceutical companies, such disposal methods as found would also extend to the part of the industry not interviewed.

There are about 10,100 metric tons per year of on-site incineration capacity. This figure is predicated on the basis of 27,200 metric tons of solvent for the pharmaceutical companies involved in organic medicinal chemical production. Not all of the in-place incinerator capacity can adequately handle air and water pollution control for all waste solvents. Often, because of stack emissions or potential equipment corrosion, halogenated solvents are not handled in on-site incinerators. Since liquid incinerators are relatively new to the pharmaceutical industry, potential problem wastes are often sent to outside contractors for incineration.

Off-site incineration techniques range from excellent to poor. There are numerous contract disposal and recycling operations across the country that are well designed and operated.

#### 4.2.2.2.2 Inorganic Medicinal Chemicals

There are no known significant amounts of waste solvents or organics from this industry section.*

#### 4.2.2.2.3 Fermentation Products

The disposal of solvents used in fermentation operations is in the form of a solvent concentrate from the solvent-recovery operations. This material, which may contain as much as 50 percent of organic solids, is hazardous, mainly because of its flammability.

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*Section 3.2.1.2.2 discusses wastes from this industry segment.

Approximately 12,000 metric tons of waste solvent concentrate from fermentation operations is disposed of annually. We estimate that all of the concentrate is incinerated either on-site or by contractors off-site. The trend is toward on-site incineration. Some plants which are currently sending these materials out to contractors for disposal have incineration units being designed, on order, or under construction. This incineration is very straightforward, as is evidenced by the number of on-site units.

The study encompassed approximately 65 percent of the U.S. fermentation capacity. On the basis of the estimated 12,000 metric tons per year of waste solvent concentrate, there is approximately 5000 metric tons per year of on-site incineration capacity. Most of the in-place incinerators have adequate air and water pollution control equipment. This essentially means particulate control only. However, since most fermentation operations are also associated with other active ingredient manufacturing operations, there is generally co-incineration of the wastes which may dictate additional pollution control requirements. Approximately 7000 metric tons (1.5 million gallons) per year is sent to outside contractors for incineration. A typical charge for this material would be $0.30 per gallon.

#### 4.2.2.2.4 Botanicals

Nearly 1200 metric tons (310,000 gallons) of waste solvent are estimated to be disposed of annually by operations producing botanicals. Three types of solvent wastes are produced in extracting alkaloids from plant material. The first solvent waste is a non-halogenated solvent concentrate containing water plant extract and organic acid salts. The second solvent waste is a concentrate of the water-immiscible chlorinated solvent used to extract the alkaloid from the first solvent. The third, a non-halogenated solvent waste, is generated in the purification of the crude alkaloid. The first ends up both with water, plant extract, and organic acid salts and as a more concentrated non-halogenated solvent stream. The second is used to extract the alkaloid from the first solvent. Water-immiscible chlorinated solvents are used for the second solvent. The chlorinated solvent is five percent of the total. These waste solvents are either incinerated on-site or by contractors off-site. We estimate that 60 percent are incinerated by contractors off-site.

#### 4.2.2.2.5 Drugs from Animal Sources

The waste solvent from the operation of obtaining medicinals from animal glands is an aqueous solvent containing as much as 50 percent water and 25 percent organic solids. The 800 metric tons (220,000 gallons) of waste solvent are generally incinerated or, when the amount is small, treatment in a biological wastewater treatment facility provides environmentally adequate disposal.

#### 4.2.2.2.6 Biologicals

Much of the solvent from biological operations is recoverable. An industry total of 250 metric tons (60,000 gallons) must be disposed of from biological operations. It is incinerated on-site or by contractors off-site. We estimate that 60 percent is handled by contractors off-site.

### 4.2.3 Present Treatment/Disposal Technologies for Organic Chemical Residues

In many instances, little is known about the constituents in organic chemical residues. The recovery operations which produce many of them are used for many various solvents and products. The residues may contain contaminants that have been removed from the product, non-reclaimable product, and other materials. Since these residues are so varied, the trend in the pharmaceutical industry has been to incinerate them. Extensive testing will be needed if these materials are to continue to be landfilled. Table 4.2.3 shows the total organic chemical residues and indicates the various methods by which they are disposed.

**TABLE 4.2.3**

**ORGANIC CHEMICAL RESIDUE DISPOSAL METHODS†**

| | | Current Disposal Methods | | | |
|---|---|---|---|---|---|
| | | On-Site | | Off-Site | |
| **Industry Segment** | **Total Hazardous Waste (metric tons per year)** | **Incineration** | **Other*** | **Incineration by Contractor** | **Landfill by Contractor** |
| **R&D** | Nil | – | – | – | – |
| **Active Ingredient Production** | | | | | |
| Organic medicinal chemicals | 13,600 | 5,440 | 1,360 | 3400 min.<br>6800 max. | 3400 max. |
| Inorganic medicinal chemicals | Nil | – | – | – | – |
| Fermentation products | Nil | – | – | – | – |
| Botanicals | Nil | – | – | – | – |
| Drugs from animal sources | Nil | – | – | – | – |
| Biologicals | Nil | – | – | – | – |
| **Formulation & Packaging** | 0 | – | – | – | – |
| Total | 13,600 | 5,440 | 1,360 | 3400-6800 | <3,400 |

*About 10 percent of the residues are disposed of on-site by other methods, such as mixing with plant wastewater prior to its treatment

†**Source:** Interviews and Arthur D. Little, Inc. estimates.

#### *4.2.3.1 Research and Development*

Organic chemical residues from research and development are disposed of with the waste solvents. This means that they are either sent for incineration by a contractor, or are incinerated in company-owned facilities that are associated with the manufacturing operations.

### *4.2.3.2 Production of Active Ingredients*

#### 4.2.3.2.1 Organic Medicinal Chemicals

Organic chemical residues from organic medicinal chemical production are generally incinerated. Approximately 40 percent of the active ingredient producers have on-site incineration for their residues. This is becoming increasingly true since these residues are seen as potential problems. Consequently, plant personnel are removing less solvent than the common previous practice to maintain pumpability for liquid type incineration. Another 25 to 50 percent utilize off-site incineration contractors. Tracing the ultimate disposal of these materials is difficult. Some are incinerated by the contractor, while others are landfilled in containers by the contractor. In addition, about another 10 percent utilize other methods of disposal, such as mixing with plant wastewater prior to its treatment.

#### 4.2.3.2.2 Inorganic Medicinal Chemicals

There are no organic chemical residues from these operations.

#### 4.2.3.2.3 Fermentation Products

The solvent concentrate from fermentation operations is discussed as a waste solvent in this report (see Section 4.2.2.2.3).

#### 4.2.3.2.4 Botanicals

There are no significant amounts of organic chemical residues from this industry segment. They are either handled with waste solvents or are sent to biological treatment or landfill.

#### 4.2.3.2.5 Drugs from Animal Sources

There are no significant amounts of organic chemical residues from this industry segment. They are either handled with waste solvents or are sent to biological treatment or landfill.

#### 4.2.3.2.6 Biologicals

There are no significant amounts of organic chemical residues from this industry segment. They are either handled with waste solvents or are sent to biological treatment or landfill.

### 4.2.4 Present Treatment/Disposal Technologies for Potentially Hazardous High Inert Content Wastes (Such as Filter Cakes)

While high inert content wastes may show up in small amounts in the R&D segment of the industry, by far the bulk occurs in the production of organic medicinal active ingredients. Generally, they are handled in the same manner no matter which type of active ingredient is being produced. Most are landfilled, but a growing percent is being incinerated to remove the organic portion. The ash is then landfilled. Table 4.2.4 shows the total high inert content wastes and indicates the various methods by which they are disposed.

Approximately 75 percent of the solid materials, such as filter cake and filter paper from organic medicinal chemical production, are disposed of in landfills. Most of these landfills are either municipal or private commercial facilities located off-site, and they are generally operated as sanitary landfills. The industry has been careful to avoid bad publicity that might accompany poor disposal techniques. Another 25 percent of the solids of this type are incinerated either on-site or off-site.

TABLE 4.2.4

HIGH INERT CONTENT WASTES DISPOSAL METHODS[†]

| | Total Hazardous Waste (metric tons per year) | Current Disposal Methods | | |
|---|---|---|---|---|
| | | On-Site | Off-Site | |
| Industry Segment | | Incineration* | Incineration* | Landfill |
| R&D | Nil | – | – | – |
| Active Ingredient Production | | | | |
| Organic medicinal chemicals | | | | |
| – Waste containing flammables only | 850 | 225 | 200 | 425 |
| – Waste containing heavy metals or corrosives | 850 | – | – | 850** |
| Total | 1,700 | 225 | 200 | 1,275 |

*Inert ash is landfilled.

**About 20 percent of the waste is neutralized, or the heavy metal is precipitated and then placed in a secure chemical landfill. Nearly 40 percent is placed untreated in a secure chemical landfill, often encapsulated in drums. The remainder goes to general landfill locations.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

### 4.2.5 Present Treatment/Disposal Technologies for Heavy Metal Wastes

ADL has surveyed pharmaceutical active ingredient manufacturers producing an estimated 20 to 40 percent of the heavy metal wastes. Table 4.2.5 shows the total heavy metal wastes and indicates the various methods by which they are disposed.

**TABLE 4.2.5**

**HEAVY METAL WASTE DISPOSAL METHODS**[†]

| Industry Segment | Total Hazardous Waste (metric tons per year) | Current Disposal Methods | | |
|---|---|---|---|---|
| | | On-Site | Off-Site | |
| | | | Recovery | Landfill* |
| **R&D** | Nil | – | x | – |
| **Active Ingredient Production** | | | | |
| Organic medicinal chemicals | 2,675 | – | 575 | 2,100 |
| Inorganic medicinal chemicals | 200 | – | – | 200 |
| Total | 2,875 | – | 575 | 2,300 |

*Heavy metal is converted to its most insoluble form, and is generally drummed and placed in a secure chemical landfill.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

With the exception of recovered R&D wastes and some large amounts of zinc and chromium wastes that are sent off-site for recovery, the heavy metal wastes are usually too dilute or contaminated for recovery. The number of facilities using heavy metals within the pharmaceutical industry is limited. Production appears to be exclusively with the larger companies. Most non-recovered heavy metal wastes are landfilled. Zinc oxide is a relatively stable and insoluble form of zinc, and much of the landfilled zinc takes this form.

Arsenic is landfilled in drums with the surrounding soil conditioned with lime to inhibit its change to a soluble form in case a drum develops a leak. The landfilled selenium wastes are dilute (an estimated 0.2 percent selenium sulfide). Mercurial wastes, generally as amalgams, are landfilled. A number of heavy metal wastes are deep-well disposed in Michigan where state approval can be obtained.

### 4.2.6 Present Treatment/Disposal Technologies for Returned Goods and Reject Material from Formulation

Returned goods (as described in Section 3.2.1.3) are handled specifically by the formulating and packaging operations of a company. Table 4.2.6 shows the total returned goods and reject material and indicates the various methods by which they are disposed.

## TABLE 4.2.6

## DISPOSAL METHODS FOR RETURNED GOODS AND REJECT MATERIAL[†]

| | Total Hazardous Waste (metric tons per year) | Current Disposal Methods | | |
|---|---|---|---|---|
| | | On-Site | | Off-Site |
| Industry Segment | | Incineration | Other[*] | Landfill[**] |
| Formulation and Packaging | 500 | 50 | 100 | 350 |

[*] Material is crushed and slurried with water, and the resulting slurry is sent to a biological wastewater treatment facility.

[**] The waste is crushed on-site to form a sludge or cake before it is sent to off-site landfill.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

Handling the amounts of pharmaceuticals that have been returned – for instance because they have reached their expiration date – requires care. Some returned goods can be salvaged, but of the returned goods that are non-salvageable, somewhere in the range of 60-80 percent are crushed in special equipment on-site to form a sludge or cake, which is then sent to a landfill off-site. The remainder is either incinerated on site, or crushed and slurried with water which is sent to an activated sludge treatment facility on-site, while the glass, metal, rubber, and cardboard are sent to a landfill off-site. Numerous types of crushers are used. Some of the names include Somat, Wascon, Rodeva, and Cumberland.

The disposal of pharmaceuticals in landfills raises many questions. Dosage levels in medicines are generally measured in milligrams; nevertheless, because many of the products may have biological or physiological effects on the environment and on man, disposal of these wastes must be carefully controlled. Because of the Drug Enforcement Agency's strict regulation on the disposal of controlled substances, there is little chance that controlled materials would be scavengable from any landfilled wastes.

Fearing the possibility of bad publicity from the scavenging of a returned good, each pharmaceutical firm has extended the care in handling controlled substances (such as narcotics) to the disposal of non-controlled substances as well. Representatives of the company witness the destruction of returned goods, whether on-site or off-site, to ensure that no tablet, vial, capsule, or the like is scavengable. To this extent, the disposal practices of the industry are excellent. Yet, little is known of the effect of such items on the landfill and the potential for hazardous quantities to leach into groundwater or streams. In this study, in an attempt to provide some basis from which to work, we used the toxicity of the active ingredients to assess the hazard.[*] However, additional work in this area is advisable.

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[*] Section 3.1.3 discusses the properties of these materials.

### 4.2.7 General Description of Treatment and Disposal Technologies

Treatment processes should reduce the volume, separate components, detoxify, and recover as much as possible for reuse. In general, no single process can adequately perform these functions. Table 4.2.7-A presents those treatment and disposal technologies found within the pharmaceutical industry, and each is discussed in the subsections which follow.

In order to fully utilize the information obtained in the study,* those processes which treat liquid effluent streams have been viewed as waste-producing steps rather than as waste-treatment steps. Table 4.2.7-B presents the processes, their functions, and the types of wastes treated.

#### *4.2.7.1 Segregation of Wastes*

There is great need to segregate wastes to obtain optimum waste treatment and disposal. Not only is segregation necessary for recovery, treatment, and disposal, it is also necessary for safe handling, transport, and treatment. Use of a system of chemical compatibility which was developed by the National Academy of Sciences has been proposed for use as a guide for the compatibility of waste materials.** Usually the same handling techniques are required for wastes as for the raw materials.

#### *4.2.7.2 Incineration of Halogenated and Non-halogenated Solvents*

When high-energy content solvents with small amounts of water and solids persist through normal process-recovery operations, they are often destroyed by thermal oxidation at high temperatures in liquid injection incinerators. These units typically operate at or above 1800°F and with sufficient turbulence and time to destroy solvents effectively. If combustion is controlled, by means of excess air, for example, no air pollution control devices are needed for solvents containing only carbon, hydrogen, and oxygen. However, these liquid injection incinerators are being increasingly equipped with air pollution control systems, because solvents often contain either suspended and dissolved solids or substances which could react to form noxious gases, such as hydrogen chloride, sulfur oxides, and nitrogen oxides.

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*We had difficulty in tracing all disposal steps, and considerable overlap with the work on the water effluent guidelines' study being prepared by Roy F. Weston, Inc., occurred.

**Witt, Philip A., Jr. "Disposal of Solid Wastes," *Chemical Engineering*, October 4, 1971, p. 61.

## TABLE 4.2.7-A

## FUNCTIONS AND WASTE TYPES OF CURRENTLY USED HAZARDOUS WASTE TREATMENT AND DISPOSAL PROCESSES

| Process | Functions Performed | Types of Waste |
|---|---|---|
| • **Chemical Treatment:** | | |
| – Oxidation of sludges | Detoxification | Inorganic chemical with/without heavy metal<br>Organic chemical with/without heavy metal |
| • **Thermal Treatment:** | | |
| – Incineration of solvents<br>– Incineration of solids | Volume reduction, detoxification, disposal | Organic chemical without heavy metal<br>Biological<br>Flammable<br>Explosive |
| • **Biological Treatment:** | | |
| – Activated sludge or other biological treatment | Detoxification | Organic chemical without heavy metal |
| • **Disposal/Storage:** | | |
| – Land burial | Disposal | Inorganic chemical with/without heavy metal<br>Organic chemical with/without heavy metal<br>Biological<br>Flammable<br>Explosive |
| – Deep-well injection | Disposal | Only liquids can be disposed of in this manner; all those listed for land disposal, with the exception of explosives, are disposable in this manner with proper precautions. |
| – Ocean dumping | Disposal | Inorganic chemical with/without heavy metal<br>Organic chemical with/without heavy metal<br>Flammable<br>Explosive |
| – Engineered storage | Storage | All as in land burial |

**Source:** Colonna, R.A., and McLaren, C., "Appendix D. Hazardous Wastes," Decision-Makers Guide in Solid Waste Management, Environmental Protection Agency, 1974, p. 146.

## TABLE 4.2.7-B
## WASTE TREATMENT PROCESSES USED TO SEPARATE A WASTE† DESTINED FOR LAND DISPOSAL

| Process | Function Performed* | Types of Waste** | Resource Recovery Capability |
|---|---|---|---|
| **Physical Treatment:** | | | |
| Carbon Sorption | Se | 1, 3, 4 | Yes |
| Dialysis | Se | 1, 2, 3, 4 | Yes |
| Electrodialysis | Se | 1, 2, 3, 4, 6 | Yes |
| Evaporation | Se | 1, 2 | Yes |
| Filtration | Se | 1, 2, 3, 4 | Yes |
| Flocculation/Settling | Se | 1, 2, 3, 4 | Yes |
| Reverse Osmosis | Se | 1, 2, 4, 6 | Yes |
| Ammonia Stripping | Se | 1, 2, 3, 4 | Yes |
| **Chemical Treatment:** | | | |
| Calcination | | 1, 2 | Yes |
| Ion Exchange | Se, De | 1, 2, 3, 4 | Yes |
| Neutralization | De | 1, 2, 3, 4 | Yes |
| Oxidation | De | 1, 2, 3, 4 | Yes |
| Precipitation | Se | 1, 2, 3, 4 | Yes |
| Reduction | De | 1, 2 | Yes |
| **Thermal Treatment:** | | | |
| Pyrolysis | VR, De | 3, 4, 6 | Yes |
| Incineration | De, Di | 3, 6, 7, 8 | Yes |
| **Biological Treatment:** | | | |
| Activated Sludge | De | 3 | No |
| Aerated Lagoon | De | 3 | No |
| Waste Stabilization Ponds | De | 3 | No |
| Trickling Filter | De | 3 | No |
| **Disposal/Storage:** | | | |
| Deep-well Injection† | Di | 1, 2, 3, 4, 6, 7 | No |

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*Se – segregation    VR – volume reduction
De – detoxification    Di – disposal

**1. Inorganic chemical without heavy metal
2. Inorganic chemical with heavy metal
3. Organic chemical without heavy metal
4. Organic chemical and heavy metal
5. Radiological††
6. Biological
7. Flammable
8. Explosive

† A waste is formed either when solids must be filtered out, or when a substance must be precipitated out because of chemical incompatibility with substances underground.

†† Use and disposal of radiological wastes within the pharmaceutical industry is not discussed in this report.

**Source:** Colonna, R.A. and McLaren, C., "Appendix D. Hazardous Wastes," Decision-Makers Guide in Solid Waste Management, Environmental Protection Agency, 1974, p. 146.

The most common air pollution control device for removing acidic gases is a wet scrubber like the venturi. A significant operating cost for these incinerators may be incurred in providing the caustic scrubbing liquors for the venturi such as lime, sodium hydroxide, or ammonia for removal of halogens from off-gases. Disposal of the scrubber liquors is usually via introduction into wastewater treatment systems. This means that a significant load of dissolved solids may be imposed. Although the effectiveness of liquid injection incinerators may vary widely in the destruction of solvent-type wastes, the efficiency of destruction is relatively high in a properly operated incinerator. In general, the liquid injection incinerators need auxiliary fuel for solvents with low heating values. Consequently, the disposal costs are inversely related to the heating values of the wastes: the higher the heating value of the solvent, the lower the disposal cost. Some waste solvents can be recovered for their fuel value. The wastes then have a net worth; thus increasing attention is being given to their recovery, especially by some of the contract waste disposers that have sophisticated systems for recovery and conversion. Instead of paying for the disposal of some waste solvents, they can be sold. However, the industry often uses high heating value wastes (i.e., solvents) to destruct low heating value waste (watery wastes) in company-owned facilities. As regulations regarding disposal become stricter, an increasing number of companies are contracting for waste disposal. This is true especially where a variety of liquids as well as solid wastes must be destroyed.

### *4.2.7.3 Incineration of Solid Wastes*

The incinerator furnace provides the environment for controlled combustion of solid wastes with air. The waste is processed by controlled oxidation with the liberation of heat, producing flue or combustion gases and a residue or ash. Most incineration furnaces have either a refractory hearth to support the burning waste, or a variety of grate-type hearths which stroke the waste. Neither the stationary hearth nor the rotary kiln furnace systems have grates. The typical stationary hearth furnace has a refractory floor which may have openings to let slightly pressurized air in underneath the burning wastes. Stationary hearth furnaces are used for commercial and small industrial incinerators. For hospital wastes, they are equipped with auxiliary gas or oil burners to maintain the furnace temperature above 1200 to 1600°F. At these temperatures, the combustible solids and vapors will be completely eliminated as long as high oxygen content air is well dispersed throughout the gas. This may require auxiliary fuel burners in the secondary combustion chamber.

The rotary kiln incinerator has been used for several hundred years in the pyroprocessing industry. Unless special provisions are made for air or water cooling, the metal cylinder is lined with refractory material to prevent overheating of the metal. The movement of the solids being processed is controlled by the speed of rotation of the kiln which is inclined toward the discharge end. The rotary kiln normally requires all the air for combustion to enter with the waste at the feed end.

Because of their versatility in handling solids, sludges, and containers, rotary kiln incinerators are being used increasingly for the thermal destruction of wastes. The incinerators are used by a number of contractors and individual plants. Since the feed rates of wastes cannot be controlled closely, as is done in liquid injection incinerators, the rotary kiln incinerator usually operates less thermally efficient than the liquid injection incinerators to ensure effective destruction while meeting air pollution regulations. However, these incinerators are especially sensitive to erratic conditions, such as the rupture of containers. Any volatile substances which are released cause oxygen deficiencies in the reaction chamber and consequently smoke forms. Thus, extensive afterburner chambers and control methods are required to prevent smoke.

The most common off-gas cleaning systems for rotary kiln incinerators like those used in liquid injection incinerators are wet scrubbers. Because of their versatility in handling different forms of wastes, especially wastes with high heating values, use of the rotary kiln incinerator is expected to increase. As in the case of the liquid injection incinerator, the costs generally are inversely related to the heating value of the wastes; the higher the heating value of the waste, the lower the disposal cost. Because tarry substances take longer to burn, they will cost more to dispose of than the non-tarry substances.

Stationary grates have been used in incinerator furnaces for a long time. The original stationary grates consisted of metal bars or rails supported in the masonry sides of the furnace chamber. Subsequently, these bars were replaced with cast metal or fabricated metal grates with provisions for rotating the grate sections to permit dumping of the ash residue. Such stationary grates are still used in many of the older incinerators.

Mechanically operated grates installed in batch-type furnaces evolved from the stationary grates in batch-type furnaces. Many of the new, small-capacity incinerators still utilize batch-fed furnaces either with stationary or mechanically operated grates. Although other thermal destruction systems such as multiple hearths or fluidized beds might be used for waste disposal, especially sludges from wastewater treatment plants, filter cakes or centrifuge solids, these are not used much in the pharmaceutical industry.

Conventional incinerator furnaces are made from refractories such as fire bricks, metals, and refractory-covered metals, such as castable or fire brick refractory linings 1 to 9 inches thick.

A rotary kiln furnace may be lined either with castable refractories or with kiln blocks. Alternatively, if the kiln is unlined, it must be cooled externally with air or water with an optional water film on the inside of the cylinder. Since furnaces are subject to temperature changes, refractory linings are susceptible to damage from spalling, fluxing, or slagging. Corrosion must also be considered for any incinerator furnace material whether refractory or metal.

Many incinerator design specifications require a secondary combustion chamber. In the primary combustion chamber wastes are ignited, vaporized, and burned above the incinerator grates. The secondary combustion chamber may consist of a separate down stream chamber wherein gases emitted from the primary chamber containing soot, hydrocarbons, and other combustibles are burned. They will be completely eliminated as long as the gases in the secondary combustion chamber are heated above 1500 to 1600°F. After complete incineration of the waste, the ash residue drops into an ash chamber or chute from the end of the grate or kiln, directly into a container, onto conveyors for disposal, or into water for quenching and cooling.

Wastewater at incinerator installations comes from various sources such as chamber sluicing, the quenching of ash, and parts of the ash conveyor system, the flue gas cooling chamber, or the flue gas scrubbers. Because of the costs of water treatment facilities required to prevent water pollution, this wastewater flow is minimized. For example, ash can be quenched with air near the discharge end of the grate or in a separate ash cooler; gas can be cooled with a gas-to-air heat exchanger or by total evaporation of fine water sprays; and dry dust collection systems can be used instead of wet ones.

Acceptable ash residue can only be achieved by prudent operation. This requires teamwork on the part of the entire staff. Materials must be mixed to provide a relatively homogeneous feed stream. The furnace operator must constantly check and adjust the air ratio, the degree of agitation, the temperature of the furnace, and the residence time of the waste flowing through the furnace. Such an operation requires constant attention and, when waste is difficult to burn, waste flow may be reduced. Knowing the composition of the residue is important as a diagnostic aid to detect operational problems, determine completeness of combustion, and identify potential water pollutants.

A well operated modern incinerator will burn out 97 percent of the combustible materials. The water solubility of the residue is of interest primarily to evaluate potential groundwater pollution, because this fraction will, to some extent, be leached from the ash over long periods of time and may contaminate groundwater. Such leaching may or may not be harmful, depending upon the materials which are dissolved and the rate of solution. In general, the amount of water-soluble materials in the ash will be quite small and will reflect the composition of the waste burned and the operating practices of the incinerator. The extent to which groundwater contamination occurs depends primarily on the fill operation, the local rainfall, drainage patterns, and geology all of which vary widely. Each fill site is different.

The organic-soluble fraction of the residue will support undesirable forms of life such as insects, rodents, and bacteria. If the level of these materials is found to be over 1 percent of the residue ash, the incinerator is not being operated properly. All organic materials are combustible. Increased residence time in the furnace, high temperatures, good agitation, and proper air distribution will reduce these materials to less than 1 percent of the residue ash. To determine if living organisms are in the ash, samples of the ash can be incubated. If organisms are present, they should be classified to establish which fraction is pathogenic. Fungi or bacteria indicate that burn out of the ash is not complete.

The air pollutants associated with incinerators fall into three categories: particulates (both mineral and combustible), combustible gases (which include carbon monoxide and hydrocarbons), and non-combustible gases (including nitrogen oxides, sulfur oxides, and hydrogen chloride).

### *4.2.7.4 Land Disposal*

The disposal methods used by many industries are those used for residential and commercial wastes: landfill and incineration. Landfills are either dumps, land burial operations, or sanitary landfills. Dumps and land burial operations are generally unsuitable disposal methods, land burial being a dump that is covered. Sanitary landfilling is defined as an engineering method of disposing of solid waste on land in a manner that minimizes environmental hazards by spreading the waste in thin layers, compacting the wastes to the smallest practical volume, and applying the compacting cover material at the end of each operating day.

Where land is available, a sanitary landfill is usually more cost-effective than incineration for disposing of solid wastes. A number of pharmaceutical companies are located in areas where land availability is not a problem. On the other hand, in areas such as New Jersey, there is increased difficulty in locating landfill operations willing to accept industrial wastes.

Current practice dictates that the potential sanitary landfill site be examined for soil condition and proximity of groundwater. Because so little is known of the properties of chemical wastes in landfills, an effective monitoring system for toxic waste disposal areas may become a routine requirement.

A safety hazard exists with landfilling organic waste. Fires and explosions occur in landfills which handle liquid organics. Further, the California Water Pollution Control Board found that water that has gone through landfilled incinerator ash will leach alkalies and salts from the fill. Gases such as methane, ammonia, and hydrogen sulfide are produced in land disposal areas. Because landfilling of materials with high water content can produce adverse effects within a landfill, States such as Indiana and New Jersey are considering, or have instituted, strict requirements on landfill operations. As regulations on a State and local level become effective, the number of landfills accepting organic liquids is expected to decrease.

Increased consideration will be given to thermal destruction as regulatory agencies establish more stringent rules and regulations for landfill disposal. There are economic reasons for landfill disposal. Costs of landfilling range from $4 to $10/ton of solids because of relatively low capital investment and energy requirements, while incineration costs fall in the range of $25 to $50/ton of solids. Incineration of solid wastes is capital- and energy-intensive. Additional fuel is required when the wastes have low heating values. Therefore, in spite of increasing pressure to minimize landfill, the rapidly escalating energy costs and capital investment requirements for thermal destruction will mean that landfill costs will continue to be more economically attractive than thermal destruction.

Secure chemical landfills (i.e., lined landfills, limited to chemical wastes, with adequate local soil conditions and often using leachate control) will probably be an important aspect of long-term disposal of selected pharmaceutical wastes. Inorganic salts and other substances, such as metallic compounds, which cannot be converted into innocuous substances will present continuing disposal problems. The magnitude of these problems will be determined by the volume and toxicity of the substances. Among these problem wastes are mercury, arsenicals, chromium, copper, and zinc. Since some of these substances, such as mercury, arsenic, and zinc would be vaporized in thermal destruction facilities, and perhaps widely dispersed by atmospheric transport, careful consideration must be given to the methods for their disposal. The "concentrate and contain" philosophy of land disposal will have to be exercised for these wastes which cannot be altered in toxicity or hazardousness.

### *4.2.7.5 Recovery for Reuse*

There are many processes for resource recovery. Important factors in deciding which method to use include type, form, and volume of waste, as well as the economics of the processes. Solvents are now recovered for economic reasons. Heavy metals, on the other hand, may be removed to keep them out of the wastes to be disposed.

Within the pharmaceutical industry, most recovery operations, with the exception of solvent recovery, are performed off-site by contractors. In our study, we found that firms handling recovery were often reluctant to discuss the source and potential market for recovered materials. The competition for recovery appears to be great in areas such as New Jersey and Illinois.

### *4.2.7.6 Wet Oxidation*

Wet oxidation is oxidation of organic materials in a liquid state under high pressure at moderate temperatures. Sulfur, nitrogen, and halogen breakdown products are retained in the liquid effluent. Waste treatment techniques, such as wet oxidation, are found infrequently in the pharmaceutical industry. However, this particular technique is used when the total energy content of the wastes is too low for cost-effective incineration. In wet oxidation a complex mixture of organic materials may be degraded to a more simple series of components which are amenable to further treatment by well-established processes such as biochemical treatment. This method is usually employed for slurries and sludges with the concomitant need to dispose of solids which, of course, are much more stable and of less potential environmental concern than the original waste. This process may be a candidate for those wastes which have inhibitory effects on biochemical systems. Its utilization will require an assessment of the specific waste compositions. Treatment costs range from $1 to $20 per thousand gallons.

#### *4.2.7.7 Deep-well Injection*

Deep-well injection for disposal of industrial wastes became popular during the late 1950's. Of the approximately 300 wells drilled in the United States, close to 200 are still in use, mostly in Texas and Michigan. To be effective the wells must have a complete and permanent separation between the stratum being used for disposal and useful strata. The rock must have the desired porosity and permeability at the level the waste is to be injected. Approximately 30 new wells are being built each year. Deep-well injection is a method of aqueous liquid waste disposal. It was investigated because a limited number of pharmaceutical plants manufacturing active ingredients use deep-well injection for their wastewater, and often solid wastes are formed while preparing the liquid for injection. In addition, if deep-well injection were to be banned, these companies would have to find some alternate method of disposal. The pollutants typically sent to deep-wells are difficult to remove using standard biological methods. Chemical methods such as precipitation or adsorption would probably be used, forming a potentially hazardous solid waste for land disposal.

Since Michigan's Department of Natural Resources officials have indicated that deep-well injection will continue, we investigated only those solid wastes produced prior to injection to meet the limitations of deep-well disposal. That is, wastes must be compatible with the brine naturally occurring in the selected porous rock stratum. If they are not compatible, solids which can plug the pores of the rock will precipitate. For example, if the stratum were a limestone, sulfates, phosphates, and aluminum salts would not be compatible.

### 4.3 ANALYSIS OF ON-SITE/OFF-SITE DISPOSAL METHODS

The pharmaceutical industry makes extensive use of waste disposal contractors. Eighty-five percent of the pharmaceutical industry's total process waste and 60 percent of the hazardous wastes are disposed of off-site by contractors. Contractors either haul and dispose of the wastes, or in areas such as northern New Jersey, trucking firms transport the waste from the pharmaceutical plant to the disposer. Within the State of New Jersey independent licenses are granted for transporting wastes and disposing of wastes. Occasionally, the pharmaceutical company delivers the waste to the disposal site.

Waste disposal contractors contacted indicated that pharmaceutical companies segregated their wastes and provided information on the constituents' characteristics and recommended handling techniques. Their work relationship appears to be open and functional. The pharmaceutical companies take considerable care to ensure that reliable methods of final disposal are used by their contract disposers. Hazardous wastes are usually landfilled in areas of low soil permeability, and are often encapsulated and segregated from other wastes.

Contract disposers are very visible and are rapidly coming under the strict regulations of air, water, and hazardous waste authorities. Because contract disposal operations are susceptible to shutdowns that can last hours or months, the larger pharmaceutical companies are tending toward installation of their own liquid and solid incineration capacity.

A large amount of the general process wastes, such as mycelia from fermentation, is landfilled. Most of the landfilling is handled by private commercial operations. In total, about 80 percent of the pharmaceutical industry process wastes disposed of by contractors are landfilled. Some of the remaining wastes are recovered, but most are incinerated. Eighty-five percent of the hazardous waste handled by contractors are incinerated or recovered. Most of this waste is solvent. While some contractors are set up to recover valuable products from this waste, most is incinerated. Most of the remainder of the hazardous wastes are landfilled. These wastes include potentially hazardous high inert content wastes, such as filter cakes, and heavy metal wastes.

Of those hazardous process wastes disposed of on-site, all except 8 percent are incinerated either in liquid injection incinerators or in solid-waste incinerators.

Table 4.3 summarizes current on-site/off-site disposal methods and indicates the amount of wastes by specific category.

## 4.4 SAFEGUARDS USED IN DISPOSAL

Numerous safeguards were found to be used in waste disposal. Table 4.4 summarizes the use of the various safeguards.

## 4.5 TREATMENT AND DISPOSAL TECHNOLOGY LEVELS AS APPLIED TO LAND-DESTINED HAZARDOUS WASTE STREAMS FROM THE PHARMACEUTICAL INDUSTRY

The various levels of technology within the pharmaceutical industry are described in this subsection for those hazardous waste streams identified in Section 3. They are described on the basis of EPA definitions for the industry studies:

> *Technology Level I* – This level encompasses the broad average of technologies which are currently used in typical facilities. There may be more than one Level I technology used by the facilities in an industry section. Although the possible variations within a technology are often numerous, Level I is defined broadly to distinguish between technologies such as incineration and landfill or chemical landfill and sanitary landfill.

## TABLE 4.3

## ANALYSIS OF ON-SITE/OFF-SITE DISPOSAL METHODS[††]

| | | Current Disposal Methods | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | On-Site | | | | Off-Site (Contractors) | | | | | |
| | Total Hazardous Waste (metric tons per year) | Incineration | | Other | | Incineration | | Landfill | | Recovery* | |
| Industry Segment | | Quantity | % | Quantity | % | Quantity | % | Quantity | % | Quantity | % |
| ● R&D | | | | | | | | | | | |
| Solvent | 1,500 | 450 | 30 | – | – | 1,050 | 70 | – | – | – | – |
| Animals | – | x | – | x** | – | – | – | – | – | – | – |
| Heavy metals | – | – | – | – | – | – | – | – | – | x | – |
| ● Active Ingredient Production | | | | | | | | | | | |
| – Organic medicinal chemicals | | | | | | | | | | | |
| Non-halogenated waste solvent | 23,800 | 9,300 | 40 | – | – | 14,500 | 60 | – | – | – | – |
| Halogenated waste solvent | 3,400 | 800 | 24 | – | – | 2,600 | 76 | – | – | – | – |
| High inert content wastes | | | | | | | | | | | |
| – containing flammables only | 850 | 225 | 26 | – | – | 200 | 24 | 425 | 50 | – | – |
| – containing heavy metals or corrosives | 850 | – | – | – | – | – | – | 850 | 100 | – | – |
| Heavy metal wastes | 2,585 | – | – | – | – | – | – | 2,010 | 78 | 575 | 22 |
| Organic chemical residues | 13,600 | 5,440 | 40 | 1,360*** | 10 | 5,100 | 38 | 1,700 | 12 | – | – |
| – Inorganic medicinal chemicals | | | | | | | | | | | |
| Heavy metal wastes | 200 | – | – | – | – | – | – | 200 | 100 | – | – |
| – Fermentation Products | | | | | | | | | | | |
| Waste solvent concentrate | 12,000 | 5,000 | 42 | – | – | 7,000 | 58 | – | – | – | – |
| – Botanicals | | | | | | | | | | | |
| Aqueous solvent | 1,000 | 400 | 40 | – | – | 600 | 60 | – | – | – | – |
| Waste halogenated solvent | 50 | 5 | 10 | – | – | 45 | 90 | – | – | – | – |
| Non-halogenated solvent | 120 | 50 | 40 | – | – | 70 | 60 | – | – | – | – |
| – Drugs from animal sources | | | | | | | | | | | |
| Aqueous alcohol | 800 | 260 | 33 | 40 | 5 | 500 | 62 | – | – | – | – |
| – Biologicals | | | | | | | | | | | |
| Aqueous alcohol | 250 | 100 | 40 | – | – | 150 | 60 | – | – | – | – |
| Antiviral vaccines | 300 | 100 | 33 | 100† | 33 | 100 | 33 | – | – | – | – |
| Other biologicals (toxoids, serum) | 200 | – | – | 200† | 100 | – | – | – | – | – | – |
| ● Pharmaceutical Preparations | 500 | 50 | 10 | 100 | 20 | – | – | 350 | 70 | – | – |
| Total | 62,005 | 22,180 | 36 | 1,800 | 3 | 31,915 | 51 | 5,535 | 9 | 575 | 1 |

*Solvent recovery is a very common practice on-site at pharmaceutical plants; it has been excluded from this study as a waste treatment process. The recovery discussed here is heavy metal recovery from waste.

**Small animals are often autoclaved if they cannot be incinerated immediately.

***Dilute and sent to on-site biological wastewater treatment.

† Autoclaved.

†† Source: Interviews and Arthur D. Little, Inc., estimates.

## TABLE 4.4

## USE OF SAFEGUARDS IN DISPOSAL OPERATIONS†

| Type of Safeguard and Related Waste | Amount of Waste (Metric Tons per Year) | Percent of Waste Disposed Using Safeguard | Estimated Number of Locations Where Used | Extensiveness of Use |
|---|---|---|---|---|
| • Segregation of wastes; | | | | |
| Hazardous | 62,000 | 100 | 54 | Very |
| • Reduction of water content; | | | | |
| Mycelia (non-hazardous) | 300,000 | 100 | 19* | Very |
| • Detailed handling instructions; | | | | |
| Hazardous | 62,000 | 100 | 54 | Very |
| • Careful and informative labelling of waste containers; | | | | |
| Hazardous | 62,000 | 80 | 43 | Very |
| • Drummed disposal of hazardous wastes in landfills; | | | | |
| High inert content wastes | 1,275 | 50 | 15 | Moderate |
| Heavy metal wastes | 2,010 | 100 | 15 | Very |
| Organic chemical residues | 1,700 | 60 | 32 | Moderate |
| • Sealed landfills; | | | | |
| High inert content wastes | 1,275 | 50 | 15 | Moderate |
| Heavy metal wastes | 2,010 | 100 | 15 | Very |
| Organic chemical residues | 1,700 | 50 | 27 | Moderate |
| • Soil conditioning to inhibit conversion of a heavy metal waste to a a water soluble form; | | | | |
| High inert content wastes | 425 | 0 | 0 | No examples found |
| Heavy metal wastes | 2,010 | 20 | 2 | Slight |

*This number only includes principal fermentation installations.

†**Source:** Interviews and Arthur D. Little, Inc., estimates.

*Technology Level II* – This level includes the best technologies which are currently used in at least one pharmaceutical facility, that is, they are the soundest treatment or disposal methods on a commercial scale from an environmental and health standpoint. In some cases the technologies may be the same as in Level I. Pilot and bench-scale installations are not considered.

*Technology Level III* – This level includes the technologies which are necessary to provide adequate health and environmental protection. Existing pilot or bench-scale processes that have high potential for meeting the needs of the industry if scaled up are considered.

Tables 4.5.1-A through 4.5.5 describe the technology levels and provide relevant information such as current usage of the identified levels of technology, present adequacy, future adequacy based upon waste stream volume, composition, suitability for retrofit, non land-related environmental impact such as energy and water requirements, residual wastes finally disposed of on land, problems, limitations and reliability of the technology, implementation time, and environmental impact.

As a basis for calculating the number of facilities employing various treatment and disposal technologies, we estimated that approximately 54 company operations large enough to have significant wastes participate in the manufacture of pharmaceutical active ingredients. Another 175 operations large enough to produce significant wastes formulate and package these and other ingredients into final pharmaceutical preparations. The derived estimates of facilities using the various treatments appear in the following sections.

### 4.5.1 Treatment and Disposal Levels for Halogenated and Non-Halogenated Waste Solvents

ADL estimates that 39,470 metric tons of non-halogenated waste solvents are generated annually by the pharmaceutical industry. This amount includes 1500 metric tons from research and development, 23,800 metric tons from organic medicinal chemicals, 12,000 metric tons from the production of fermentation products, 1000 metric tons of aqueous solvent concentrates (720 metric tons on a dry basis) from the production of botanicals and an additional 120 metric tons of non-aqueous solvents from botanicals, 800 metric tons from the production of drugs from animal sources, and 250 metric tons from the production of biologicals.

In our survey of the industry, we found that approximately 50% of the industry facilities had onsite incineration capability; the remainder used contractor incineration to dispose of these solvent wastes. These two treatment technologies, therefore, are defined as Level I in Table 4.5.1-A. Both of these disposal techniques are presently adequate. A limitation of this kind of incineration is that liquid incinerators cannot handle a high inorganic salt content waste.

Because there are a number of contractors who provide energy and resource recovery at their own sites, we have included this technology in our Level II discussion. By energy recovery we mean that the contractor has the capability to produce steam during

### TABLE 4.5.1–A
### TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR NON-HALOGENATED WASTE SOLVENTS†

**Amount of Waste:*** 39,470 Metric Tons per Year

**Hazardous, Physical, and Chemical Properties of Waste:** Flammable organic liquid.

| | **Level I** | **Level II** | **Level III** |
|---|---|---|---|
| • **Technology** | 1) Incineration on-site<br>2) Contractor incineration | 1) As Level I<br>2) Includes energy and resource recovery at the contractor's site. | 1) As Level I***<br>2) As Level II*** |
| • **Current Usage** | | | |
| – Percent of Industry Facilities | 1) 50<br>2) 50 | 1) 50<br>2) 12 | |
| – Number of Facilities | 1) 27<br>2) 27 | 1) 27<br>2) 6 | |
| • **Risk** | | | |
| – Risk from Fires or Explosions | Moderate | Moderate | |
| – Transport Risks | Minimized with on-site incineration | Minimized with on-site incineration | |
| – Pollution Risk | Minor | Minor | |
| • **Present Adequacy** | 1) Excellent<br>2) Excellent | 1) (2) Excellent | |
| • **Future Adequacy** | 1) Good<br>2) Good | 1) Good<br>2) Excellent | |
| • **Residual Waste**** | 0 | 0 | 0 |
| • **Reliability of Technology** | 1) Good<br>2) Many reliable contract disposal firms | As Level I | As Level I |
| • **Limitations or Problems** | 1) Cannot handle high inorganic salt content<br>2) Same as 1) above | | |
| • **Suitability for Retrofit** | Excellent | | |
| • **Non-Land Related Impact** | None, excepting salt plume | | None |
| • **Implementation Time** | 1) Two years<br>2) Minimal | | Technology not yet proven for salt removal by scrubbing |

*Generated, i.e., prior to treatment or disposal (see Table 4.2.2).

**Finally land disposed.

***With scrubber for salts when they are present in concentrations that require scrubbing.

†**Source:** Interviews and Arthur D. Little, Inc., estimates.

incineration of the waste. Resource recovery is possible if the contractor produces a low-grade, salable fuel from the various waste solvents that he collects. We estimate that approximately 12% of the pharmaceutical facilities are currently using contractors which are using energy and resource recovery techniques.

The Level III technology is the same as Levels I and II, except that a scrubber is added to handle salts when they are present in concentrations that require scrubbing. Although there have been numerous attempts to work out this technological problem, there is currently no proven method for complete salt removal by scrubbing. In Table 4.5.1-B we discuss the treatment and disposal technology levels for halogenated waste solvents. There are approximately 3450 metric tons of halogenated waste solvents generated annually in the pharmaceutical industry. These materials are usually flammable and the halogen is typically chlorine.

In our survey of the industry, we found that those facilities which had incineration capability onsite either diluted the halogenated solvents with their other solvents, or they had them incinerated by a contractor. Those plants which had no incineration capability onsite also had their waste solvents incinerated by contractor. In both cases, the contractor had the capability for scrubbing for HCl. We have estimated that about 35% of the industry's facilities with this kind of solvent waste were diluting and incinerating onsite. In so doing they were meeting current air pollution control regulations. A specific limitation on this kind of incineration, however, is that it tends to corrode the incinerator. Because we had identified offsite facilities which used incineration and energy- and resource-recovery techniques, we have included energy and resource recovery as a technology level within Level II. About 10% of pharmaceutical industry facilities utilize offsite contractor incineration with energy and resource recovery. As long as care is taken to maintain proper operating conditions, Level I and Level II technology provides adequate waste disposal.

It takes approximately two years to design and install an onsite incinerator within a pharmaceutical plant. However, there is an adequate supply of reliable contract disposal firms in most areas of the country. Also, under Level I we believe that the incineration onsite that is accomplished by dilution of the halogenated solvent with other solvents is satisfactory, because the use of halogenated solvents within the pharmaceutical industry does not constitute a major portion of the solvents.

### 4.5.2 Treatment and Disposal Levels for Organic Chemical Residues

Based on its 1973 production level, we estimate that the pharmaceutical industry generates 13,600 metric tons of organic chemical residues annually. By far the majority of these residues results from the production of the active ingredients used in organic medicinal chemicals. We further estimate that about 10% of these residues are disposed of onsite by methods other than incineration; for example, by mixing the residue with plant wastewater prior to its treatment. We have not cited this method as a unique technology level because we found it to be used for only a small amount of waste within a given plant, and only when

## TABLE 4.5.1–B

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR HALOGENATED WASTE SOLVENTS[†]

**Amount of Waste:*** 3450 Metric Tons per Year

**Hazardous, Physical, and Chemical Properties of Waste:** Flammable, Chlorinated Organic Liquid.

| | Level I | Level II | Level III |
|---|---|---|---|
| • **Technology** | 1) Incineration on-site (diluted with other solvents)<br>2) Contractor incineration with scrubbing for HCl | 1) as Level I***<br>2) With energy and resource recovery | 1) as Level I***<br>2) as Level II |
| • **Current Usage** | | | |
| – Percent of Industry Facilities | 1) 35<br>2) 65 | 1) 35<br>2) 10 | |
| – Number of Facilities | 1) 19<br>2) 35 | 1) 19<br>2) 5 | |
| • **Risk** | | | |
| – Risk from Fires or Explosions | 1) Moderate<br>2) Moderate | 1) Moderate<br>2) Moderate | |
| – Transport Risks | Minimized by on-site incineration | Minimized by on-site incineration | |
| – Pollution Risk | 1) Moderate<br>2) Slight | 1) Moderate<br>2) Slight | |
| • **Present Adequacy** | Good | 1) Good<br>2) Excellent | |
| • **Future Adequacy** | Good | 1) Good<br>2) Excellent | |
| • **Residual Waste**** | Nil | Nil | |
| • **Reliability of Technology** | Good | Good | |
| • **Limitations or Problems** | 1) Corrosion and pollution may occur at high percentage chlorine. | | |
| • **Suitability for Retrofit** | Good | Good | |
| • **Non-Land Related Impact** | – | – | |
| • **Implementation Time** | 1) Two years<br>2) Minimal | 1) Two years<br>2) Minimal | |

*Prior to treatment or disposal.
**Finally land disposed.
***Assuming that the relatively small percentage of halogenated solvents will continue.

[†] Source: Interviews and Arthur D. Little, Inc., estimates.

the waste was compatible with the onsite treatment. The other methods currently used to dispose of these residues are onsite and contractor incineration and landfill.

Only the smaller facilities are likely to place these materials in a landfill. We estimate that 40% of the industry facilities use onsite incineration and another 40% use contractor incineration. The present adequacy of the incineration method is excellent, while the landfill can be defined as only fair. In many instances, little is known about the constituents in organic chemical residues. For that reason we have described the future adequacy of the landfill method as poor. There is little residual waste from the incineration of these materials. Often the amount of solvent in the residue is maintained at a level that allows it to remain pumpable, so that it can be incinerated in a liquid-feed incinerator. In the past, the residue was allowed to flow into a steel drum while still hot. As the material cooled, it turned into a hard, glassy substance which was then landfilled. A potential for groundwater contamination is inherent in this method. With Level II, either onsite or contractor incineration is recommended, and Level III is the same as Level II.

Table 4.5.2 provides information on the contractor-recommended levels of treatment and disposal of organic chemical residues.

### 4.5.3 Treatment and Disposal Levels for Potentially Hazardous High Inert-Content Wastes, Such as Filter Cakes

To discuss these high inert-content wastes effectively, we divided such as filter cakes, in two classes, one of which contains flammable solvent, and the other which contains corrosives or trace amounts of heavy metals. Based on information obtained in our interviews, we estimate that approximately half of the wastes contains solvents and the other half heavy metals and corrosives. These materials are either semi-solid or solid. The inert content may be filter aid or materials, such as charcoal.

In Table 4.5.3-A, we discuss the wastes which contain flammable solvent. Currently, about one half of the plants generating this kind of waste send the material to contractor landfill. The others have some means of incinerating, generally in rotary kilns or multiple hearth furnaces. The content in these wastes ranges from under five to as much as 60 percent solvent.

The present adequacy of the landfill method is only fair and its future adequacy has been determined to be poor because of the possibility of fires in the disposal area. On the other hand, incineration provides an excellent means of making the waste inert as it burns off all solvent and the only residual is the inert ash. A facility for the incineration of these materials would take about two years to design and install.

For Level II technology, we are recommending incineration as the best method currently used. Because it provides an environmentally acceptable method for disposing of these materials, we have also stated that Level III should be incineration. In Table 4.5.3-B,

## TABLE 4.5.2

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR ORGANIC CHEMICAL RESIDUES[†]

**Amount of Waste:**[*] 13,600 metric tons per year

| | Level I | Level II | Level III |
|---|---|---|---|
| • **Technology** | 1) On-site incineration<br>2) Contractor incineration<br>3) Landfill[†] | 1) On-site incineration<br>2) Contractor incineration | as Level II |
| • **Current Usage** | | | |
| – Percent of Industry Facilities | 1) 40<br>2) 40<br>3) 20 | 1) 40<br>2) 40 | |
| – Number of Facilities | 1) 22<br>2) 22<br>3) 11 | 1) 22<br>2) 22 | |
| • **Risk** | | | |
| – Risk from Fires or Explosions | 3) Yes | Moderate | |
| – Transport Risks | 2) Moderate<br>3) Moderate | 2) Moderate | |
| – Pollution Risk | 3) Yes | Nil | |
| • **Present Adequacy** | 1) (2) Excellent<br>3) Fair | Excellent | |
| • **Future Adequacy** | 1) (2) Excellent<br>3) Poor | Excellent | |
| • **Residual Waste**[**] | 1) (2) Minimal[††] | Minimal | |
| • **Reliability of Technology** | 1) (2) Good<br>3) Unknown | Good | |
| • **Limitations or Problems** | 1) (2) None<br>3) Landfill adequacy unknown | None | |
| • **Suitability for Retrofit** | 1) Good[†††] | Good | |
| • **Non-Land Related Impact** | 3) Potential groundwater pollution | Nil | |
| • **Implementation Time** | 1) Two years | 1) Two years | |

[*] Generated, i.e., prior to treatment or disposal.

[**] Finally land disposed.

[†] Since smaller facilities are more likely to use landfilling, it is included here.

[††] If enough solvent remains to keep waste pumpable, it can be incinerated in liquid-feed incinerator with little residual waste.

[†††] Heated feed to existing liquid injection incinerator is possible.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

## TABLE 4.5.3–A

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR POTENTIALLY HAZARDOUS HIGH INERT CONTENT WASTES[†]

**(such as filter cakes, which contain flammable solvent)**

**Amount of Waste:*** 850 Metric Tons per Year

**Hazardous, Physical, and Chemical Properties of Waste:** Flammable, Semi-Solid or Solid with High Inerts Contents

| | Level I | Level II | Level III |
|---|---|---|---|
| • **Technology** | 1) Landfill<br>2) Incineration | Incineration | as Level II |
| • **Current Usage** | | | |
| – Percent of Industry Facilities | 1) 50<br>2) 50 | 50<br>27 | |
| – Number of Facilities | 1) 27<br>2) 27 | 27 | |
| • **Risk** | | | |
| – Risk from Fires or Explosions | 1) Yes | Minimal | |
| – Transport Risk | Slight | Slight | |
| – Pollution Risk | 1) Yes | Nil | |
| • **Present Adequacy** | 1) Fair<br>2) Excellent | Excellent | |
| • **Future Adequacy** | 1) Poor<br>2) Excellent | Excellent | |
| • **Residual Waste**** | 1) All<br>2) Inert ash | Inert ash | |
| • **Reliability of Technology** | 1) Unknown<br>2) Excellent | Excellent | |
| • **Limitations or Problems** | Fire risk | None | |
| • **Suitability for Retrofit** | 1) Not recommended<br>2) Good | Good | |
| • **Non-land Related Impact** | – | – | |
| • **Implementation Time** | 2) Two years | Two years | |

*Prior to treatment or disposal
**Finally land disposed

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

## TABLE 4.5.3–B

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR POTENTIALLY HAZARDOUS HIGH INERT CONTENT WASTES[†]

**(such as filter cakes, which contain heavy metals or corrosives)**

**Amount of Waste:*** 850 Metric Tons per Year

**Hazardous, Physical, and Chemical Properties of Waste:** Toxic, Semi-Solid or Solids with high inerts content (may contain solvent)

| | Level I | Level II | Level III |
|---|---|---|---|
| • **Technology** | 1) Secure chemical landfill<br>2) Sanitary landfill | Neutralize or precipitate heavy metal, then place in secure chemical landfill | as Level II |
| • **Current Usage** | | | |
| – Percent of Industry Facilities | 1) 40<br>2) 40 | 20 | |
| – Number of Facilities | 1) 22<br>2) 22 | 11 | |
| • **Risk** | | | |
| – Risk from Fires or Explosions | Slight | Slight | |
| – Transport Risks | Slight to moderate | Slight | |
| – Pollution Risk | 1) Slight<br>2) Moderate*** | Slight | |
| • **Present Adequacy** | 1) Good<br>2) Fair | Good | |
| • **Future Adequacy** | 1) Fair<br>2) Poor | Good | |
| • **Residual Waste**** | All | More stable | |
| • **Reliability of Technology** | 1) Good<br>2) Fair | Good | |
| • **Limitations or Problems** | 1) (2) Soil conditions | Soil conditions | |
| • **Suitability for Retrofit** | – | – | |
| • **Non-Land Related Impact** | – | – | |
| • **Implementation Time** | – | – | |

*Prior to treatment or disposal.

**Finally land disposed.

***Anaerobic conditions can occur in sanitary landfill which will dissolve heavy metals and make them mobile.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

we outline our evaluation of treatment and disposal of those high inert-content wastes which contain corrosives or trace amounts of heavy metals. We estimate that the pharmaceutical industry generates 850 metric tons of these wastes annually. Because they contain corrosives, they are generally not incinerated.

Because these materials cannot be incinerated, they are currently landfilled. We estimate that about 40% of the facilities dispose of these wastes in sanitary landfills, which means that wastes other than chemical wastes are being disposed of. We estimate that a second 40% disposes of these wastes in a secure chemical landfill that is both limited to chemical wastes and has to be lined with some material to ensure that materials do not leach into groundwater. The present adequacy of the sanitary landfill method is only fair and is not recommended for future disposal. Anaerobic conditions can occur in sanitary landfills which will dissolve heavy metals and make them mobile.

Secure chemical landfills provide better environmental conditions, but even these can create problems because of local soil conditions. Level II technology, which is currently used by about 20% of the facilities, involves the neutralization of the corrosive material or precipitation of the trace amounts of heavy metal. Then, the material which is less soluble and less toxic is placed in a secure chemical landfill. Because of the nature of these wastes and the inability to recover the trace amounts of heavy metal, we have recommended this Level II treatment as Level III also.

### 4.5.4 Treatment and Disposal Levels for Heavy Metal Wastes

ADL estimates that the pharmaceutical industry generates 2875 metric tons of heavy metal wastes annually. Pharmaceutical facilities which produce these heavy metal wastes are not common within the industry. In fact, we estimate that only 15 pharmaceutical plants generate heavy metal wastes. About 80% of these facilities currently convert the heavy metal wastes into their most insoluble form, place them in drums, and then bury them in a secure chemical landfill. All the plants we visited that used landfill for disposal used a secure chemical landfill for their heavy metal wastes. However, we believe that a small percentage of the heavy metal wastes may be placed in normal sanitary landfills. As we mentioned before, anaerobic conditions can occur in sanitary landfills which may dissolve the heavy metals and make them mobile.

About 20% of the industry facilities currently subject their heavy metal wastes to a recovery process at an offsite contractor location. From an environmental control viewpoint, this technique is excellent, since only a small portion of the wastes is then disposed of on land. The limitations of this kind of disposal include the economics of the recovery and the market for the recovered metal. For Level III, we recommend both the recovery as described in Level II and engineered storage. However, in our survey, we did not find anyone utilizing engineered storage. We include engineered storage in this Level III technology because there are some heavy metal wastes which do not lend themselves to recovery and therefore must be subjected to some secure method of disposal.

Table 4.5.4 provides information on our recommended levels of treatment and disposal of heavy metal wastes.

### 4.5.5 Treatment and Disposal Levels for Returned Goods and Reject Materials from Formulation

ADL estimates that the pharmaceutical industry annually generates 500 metric tons of waste from returned goods and reject material from formulation operations. The technology most commonly used within the industry for handling these wastes is to crush the material and dispose of it in a sanitary landfill. We estimated that approximately 60% of the industry facilities use this method. Because more information is needed on the effects of these materials being landfilled, we have described their present adequacy as good, but have recommended other treatment for Level II.

In Level II technology in our survey we have found that these wastes were both being incinerated by either a contractor or at a company-owned facility and also treated in an onsite biological wastewater treatment system. Approximately 10% of these facilities currently use incineration and about 20% use the biological treatment. The residual from the incineration is a non-hazardous ash.

The problems and limitations associated with these two methods involve the availability of either incineration or onsite biological treatment. We have described Level III to be the same as Level II, because we believe these two methods provide environmentally adequate methods of disposal.

Table 4.5.5 provides information on our recommended levels of treatment and disposal of returned goods.

## TABLE 4.5.4

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR HEAVY METAL WASTES††

**Amount of Waste:*** 2875 Metric Tons per Year

| | Level I | Level II | Level III |
|---|---|---|---|
| • **Technology** | Convert heavy metal to most insoluble form, drum, and place in secure chemical landfill*** | 1) Recovery off-site<br>2) As Level I | 1) Recovery off-site<br>2) Engineered storage |
| • **Current Usage** | | | |
| – Percent of Industry Facilities† | 80 | 1) 20<br>2) 80 | 1) 20<br>2) 0 |
| – Number of Facilities† | 12 | 1) 3<br>2) 12 | 1) 3<br>2) 0 |
| • **Risk** | | | |
| – Risk from Fires or Explosions | – | – | – |
| – Transport Risks | Slightly | 1) (2) Slight | 1) (2) Slight |
| – Pollution Risk | Moderate | 1) Minimal<br>2) Moderate | 1) Minimal<br>2) Slight |
| • **Present Adequacy** | Good | 1) Excellent<br>2) Good | 1) (2) Excellent |
| • **Future Adequacy** | Good | 1) Excellent<br>2) Good | 1) (2) Excellent |
| • **Residual Waste**** | All | 1) Some<br>2) As Level 1 | 1) Some<br>2) All |
| • **Reliability of Technology** | Good | 1) (2) Good | |
| • **Limitations or Problems** | Soil conditions | 1) Market for heavy metal<br>2) Soil conditions | |
| • **Suitability for Retrofit** | – | – | |
| • **Non-land Related Impact** | – | 1) Minimal | |
| • **Implementation Time** | – | 1) Two years | |

*Prior to treatment of disposal

**Finally land disposed

***All of the plants we visited that used landfill for disposal used a secure chemical landfill for their heavy metal wastes. We believe, however, that a small percentage of the heavy metal wastes may be landfilled in sanitary landfills.

†15 pharmaceutical plants are estimated to have heavy metal wastes.

††**Source:** Interviews and Arthur D. Little, Inc., estimates.

## TABLE 4.5.5

## TREATMENT AND DISPOSAL TECHNOLOGY LEVELS FOR POTENTIALLY HAZARDOUS RETURNED GOODS AND REJECT MATERIAL FROM FORMULATION[††]

**Amount of Waste:*** 500 Metric Tons per Year

| | Level I | Level II | Level III |
|---|---|---|---|
| ● **Technology** | Crush on-site and landfill in sanitary landfill. | 1) Incineration by contractor or at company-owned facility.<br>2) Treatment in on-site biological waste-water treatment system. | as Level II |
| ● **Current Usage** | | | |
| – Percent of Industry Facilities | 60 | 1) 10<br>2) 20 | |
| – Number of Facilities | 122 | 1) 15<br>2) 30 | |
| ● **Risk** | | | |
| – Risk from Fires or Explosions | None | 1) (2) None | |
| – Transport Risks | None | 1) (2) None | |
| – Pollution Risk | Slight | 1) (2) None | |
| ● **Present Adequacy** | Good | 1) (2) Excellent | |
| ● **Future Adequacy** | *** | 1) (2) Excellent | |
| ● **Residual Waste**** | All | 1) 60 percent of waste[†] | |
| ● **Reliability of Technology** | Good | 1) (2) Good | |
| ● **Limitations or Problems** | *** | 1) (2) Availability | |
| ● **Suitability for Retrofit** | – | – | |
| ● **Non-Land Related Impact** | – | – | |
| ● **Implementation Time** | – | – | |

*Prior to treatment or disposal.

**Finally land disposed.

***More information needed.

†Non-hazardous ash.

[††] **Source:** Interviews and Arthur D. Little, Inc., estimates.

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## 5.0 COST ANALYSIS

### 5.1 BACKGROUND

Total production of active ingredients within the pharmaceutical companies in 1973 is estimated at 45,000 metric tons. Overall, production of these ingredients is expected to grow at a rate of 3 percent per year through 1977 and at a 7 percent rate thereafter.* Waste generated and destined for land disposal in 1973 for the pharmaceutical industry is estimated at 244,000 metric tons per year. The hazardous waste represents about 25 percent of the total waste or 61,000 metric tons per year in 1973. Wastes are expected to grow to 400,000 metric tons per year of total wastes and to 100,000 metric tons per year of hazardous wastes by 1983. Approximately 85 percent of total wastes and 60 percent of hazardous wastes are estimated to be treated and disposed of by contractors.

Approximately 54 company operations estimated to be large enough to have significant wastes participate in the manufacture of pharmaceutical active ingredients. Another 175 operations large enough to produce significant wastes formulate and package these and other ingredients into final pharmaceutical preparations. In order to calculate total industry costs, we used the above estimates of company operations in conjunction with industry production estimates and treatment and disposal costs per ton of product.

### 5.2 SUMMARY OF COSTS FOR CONTROLLED TREATMENT AND DISPOSAL OF LAND-DESTINED HAZARDOUS WASTES

Tables 5.2-A, -B, and -C summarize the costs of end-of-pipe treatment and disposal systems either currently in use or recommended for future use in pharmaceutical production facilities. No costs are given for in-process changes made to minimize or change the hazardous character of the wastes. Because typical plants were used to develop an estimate of the total industry cost of treatment and disposal of hazardous wastes, the total industry costs should be taken only as an indication of the order of magnitude of such costs rather than as the outcome of a detailed industry survey of the costs. Issues such as site specific costs, different products or product mixes, local disposal rates, and available disposal methods were not included in this estimate. Where it is necessary to reflect different economics of large versus small plants and separate hazardous waste streams, costs have been developed typically for more than one plant in each industry section. These product-specific analyses are presented in Tables 5.4.2.1 to 5.4.3.

### 5.3 RATIONALE AND REFERENCES USED IN COST ESTIMATING

Eighty-five percent of the total pharmaceutical industry process waste are disposed of through contractors. The onsite disposal facilities are liquids incinerators and solids incinerators. However, almost 70 percent of the incineration capability are located offsite with contractors. There is, however, a trend toward onsite incineration. In our survey, we contacted numerous pharmaceutical companies that had recently installed incineration capacity or were planning installation. Because of the patterns of offsite disposal, costs in this report have usually been determined for representative plants on the basis of contractor disposal. In addition, there is information presented on the cost of onsite incinerators for solids. The data are presented for various size ranges. Installation of these units is usually determined by individual company location and policy. Where industry in an area is sparse, there may be limited availability of contractor incineration. On the other hand, in some areas, pharmaceutical companies may find an adequate supply of disposers, but find that they are constantly on the brink of being shut down by local regulatory agencies for air or water regulation violations. These pharmaceutical companies may decide in favor of onsite incineration to ensure that they have a reliable disposal method.

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*The industry growth rate is discussed in Section 2.7.

### TABLE 5.2-A

### PERSPECTIVE ON THE PHARMACEUTICAL INDUSTRY: TREATMENT AND DISPOSAL COSTS PER UNIT OF HAZARDOUS WASTE[†]

**($/metric ton)**

| Product Category | Level I | Level II | Level III |
|---|---|---|---|
| ● Bulk Active Ingredient | | | |
| – Organic Medicinal Chemicals | | | |
| Non-halogenated waste solvent | 68 | 68 | 68 |
| Halogenated waste solvent | 184 | 184 | 184 |
| High inert content wastes | 26 | 43 | 43 |
| Heavy metal waste | 50 | 50 | 60 |
| Organic chemical residues | 100 | 100 | 100 |
| – Inorganic Medicinal Chemicals | | | |
| Heavy metal waste | 50 | 50 | 60 |
| – Fermentation Products | | | |
| Waste solvent concentrate | 120 | 120 | 120 |
| – Botanicals | | | |
| Aqueous solvent | 144 | 144 | 144 |
| Waste halogenated solvent | 180 | 180 | 180 |
| Non-halogenated waste solvent | 68 | 68 | 68 |
| – Drugs from Animal Sources | | | |
| Aqueous alcohol | 142 | 142 | 142 |
| – Biologicals | | | |
| Aqueous alcohol | 142 | 142 | 142 |
| Antiviral vaccine | 30 | 30 | 30 |
| Other biologicals (toxoids, serum) | 30 | 30 | 30 |
| ● Pharmaceutical Preparations | 28 | 67 | 67 |

[†] **Source:** Arthur D. Little, Inc., estimates.

## TABLE 5.2-B

## PERSPECTIVES ON THE PHARMACEUTICAL INDUSTRY: HAZARDOUS WASTE TREATMENT AND DISPOSAL COSTS*[†]

| | Estimated Total Annual Costs ($000)** | | |
|---|---|---|---|
| **Product Category** | **1973** | **1977** | **1983** |
| ● Bulk Active Ingredient | | | |
| – Organic Medicinal Chemicals | | | |
| Non-halogenated waste solvent | 1,620 | 1,820 | 2,585 |
| Halogenated waste solvent | 630 | 705 | 1,000 |
| High inert content wastes | 45 | 80 | 110 |
| Heavy metal wastes | 145 | 160 | 275 |
| Organic chemical residues | 1,360 | 1,530 | 2,170 |
| – Inorganic Medicinal Chemicals*** | | | |
| Only one hazardous waste identified | – | – | – |
| – Fermentation Products | | | |
| Waste solvent concentrate | 1,440 | 1,620 | 2,300 |
| – Botanicals | | | |
| Aqueous solvent | 145 | 160 | 230 |
| Halogenated waste solvent | 10 | 10 | 15 |
| Non-halogenated waste solvent | 10 | 10 | 15 |
| – Drugs from Animal Sources | | | |
| Aqueous alcohol | 115 | 130 | 180 |
| – Biologicals | | | |
| Aqueous alcohol | 35 | 40 | 60 |
| Antiviral vaccines | 10 | 10 | 15 |
| Other biologicals (toxoids serum) | 5 | 10 | 10 |
| ● Pharmaceutical Preparations | 15 | 40 | 50 |
| Partial Total[+] | 5,585 | 6,325 | 9,015 |

*Based on average treatment costs and pharmaceutical industry waste estimates.

**December 1973 dollars.

***Included in heavy metal wastes under organic medicinal chemicals

[+] Excludes R&D costs.

[†] **Source:** Arthur D. Little, Inc., estimates.

## TABLE 5.2-C

## PERSPECTIVES ON THE PHARMACEUTICAL INDUSTRY: COST IMPACT OF HAZARDOUS WASTE TREATMENT AND DISPOSAL[†]

| Product Category | 1973 Selling Price $/kg | Estimated Hazardous Waste Control Cost as Percent of Price[*] | | |
|---|---|---|---|---|
| | | Level I | Level II | Level III |
| • Bulk Active Ingredient | | | | |
| Organic Medicinal Chemicals | 22 | 0.2% | 0.22% | as Level II |
| Inorganic Medicinal Chemicals[**] | – | – | – | – |
| Fermentation Products | 44 | 0.34% | as Level I | as Level I |
| Botanicals | [***] | <0.1% | as Level I | as Level I |
| Drugs from Animal Sources | [***] | | | |
| Biologicals | [***] | | | |

[*] Manufacturers selling price in the case of pharmaceutical preparations; value of sales, that is, the net selling value FOB plant or warehouse, or delivered value, whichever represents the normal practice for bulk active ingredient.

[**] Representative data not available because most inorganic medicinal ingredients that might produce a hazardous waste are purchased from the chemical industry.

[***] Data not available; the selling price of many of these products is stated in terms of biological activity.

[†] Source: Arthur D. Little, Inc., estimates.

In each of the representative operation cost analyses, typical plant situations are identified in terms of production capacity, process waste load, hazardous waste load, and product value. Annual capital costs have been assumed to be a constant percentage (10 percent of fixed investment). Depreciation costs have been calculated on the straight-line method (10 percent per year) over 10 years, even though the physical life is longer. Taxes and insurance are included as 1-1/2 percent of the capital investment. All estimates are reported in December 1973 dollars. The Engineering News Record (ENR) Construction Cost Index (1158) and the Chemical Engineering (CE) Plant Cost Index (148.2) have been used to prepare these estimates. Land requirements for onsite treatment are not significant; therefore, no cost allowance has been made. Offsite treatment and disposal land requirements are not considered directly. Land costs are included in the contractor's charges. Cost-effectiveness relationships are implicit in the calculation of these costs, together with the technology levels achieved. For example, when considering a small pharmaceutical plant, the use of contractor disposal is more cost-effective because of the economies of scale and the potential for energy and resource recovery. With larger pharmaceutical operations, onsite and offsite incineration have approximately equal cost-effectiveness. The major issue in these instances would be the availability of capital.

**Table 5.3-A presents costs for transporting wastes for offsite disposal:**

### TABLE 5.3-A

### COST OF TRANSPORTING WASTES[†]

| Distance (miles) | Liquids ($/m$^3$) | ($/1000 gal) | Solids ($/metric ton) |
|---|---|---|---|
| 5 | 0.92 | 3.50 | 1.85 |
| 10 | 1.02 | 3.85 | 2.10 |
| 20 | 1.48 | 5.60 | 2.70 |
| 40 | 1.94 | 7.35 | 3.40 |
| 50 | 2.03 | 7.70 | 3.70 |

[†] **Source:** Arthur D. Little. Inc., estimates.

**A number of contractors were contacted in this study, primarily in EPA Regions II and V where concentrations of the pharmaceutical industry are found. Table 5.3-B summarizes the information obtained, supplemented and checked by ADL estimates. No factors are included for areas of the country, as no obvious differences were found in our analysis.**

### TABLE 5.3-B

### CONTRACT DISPOSAL CHARGES FOR HAZARDOUS WASTES[†]

| Method | $/Metric Ton |
|---|---|
| General Landfill* | 8 |
| Secure Chemical Landfill** | 17 |
| Approved Secure Landfill*** | 30 |
| Incineration | |
| Non-halogenated solvents (organic content 85% and over) | 90 |
| Solids | 30 |
| Neutralization (or precipitation of components) of Wastes | 30 |

*Operated as sanitary landfill.

**Lined landfill limited to chemical wastes.

***Lined landfill limited to hazardous wastes with monitoring.

[†] **Source:** Interviews and Arthur D. Little, Inc., estimates.

Also, the costs for offsite disposal vary, depending upon the amount of waste to be disposed, the collection frequency, and the onsite storage facilities. Figure 5.3-A gives an example of how these factors affect costs. Figure 5.3-B presents capacity ranges and investment costs for industrial solid waste incinerators, and Table 5.3-C presents background information. Figure 5.3-C gives operating costs in terms of dollars per metric ton.

## 5.4 COSTS FOR TREATMENT AND DISPOSAL OF HAZARDOUS WASTES

### 5.4.1 Research and Development

The hazardous wastes produced within the R&D section of the industry include both waste solvents and test animals. Waste solvents can be incinerated either by contractors or in company-owned facilities for about $0.30 per gallon. A research facility with 100 researchers will produce about 2000 gallons of waste solvent annually. The cost of incinerating that waste will be approximately $600 annually.

Most pathological incineration capacity for test animals within the R&D section of the industry is installed. It is not discussed here.

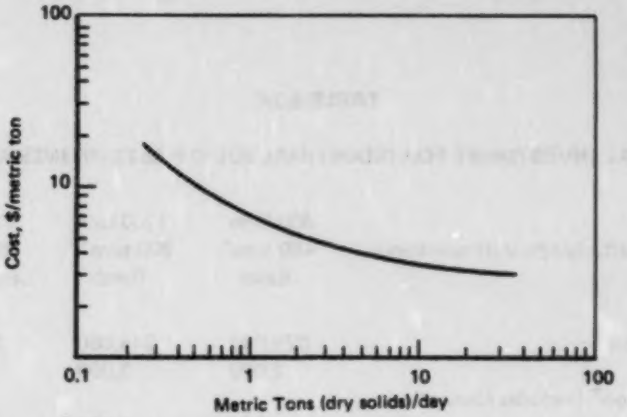
### 5.4.2 Production of Active Ingredients (SIC 2831 and 2833)

#### *5.4.2.1 Organic Medicinal Chemicals*

Of the 27,200 metric tons of waste solvent produced by the pharmaceutical companies in the manufacture of organic medicinal chemicals, about 10,100 metric tons per year can be incinerated onsite by the industry. Onsite incineration capacity and its associated pollution control equipment (both air and water) are expected to increase.

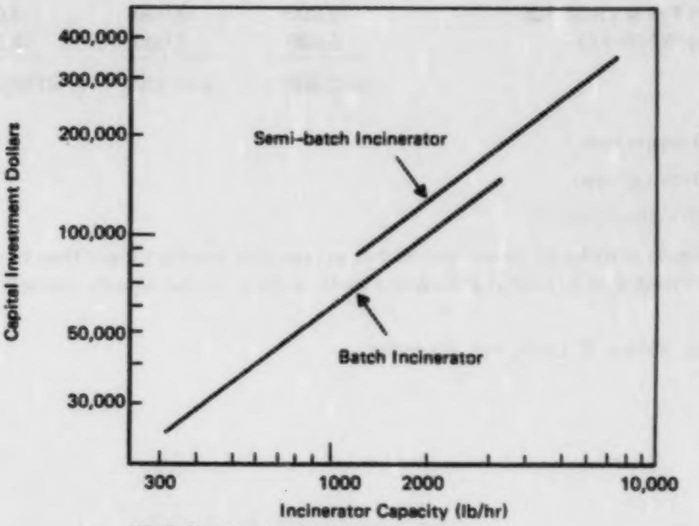
Offsite contractors dispose of the remainder of the waste solvent, about 17,100 metric tons per year. After surveying the disposers, we found the typical charge for incineration of pharmaceutical waste solvents to be $0.20 to $0.35 per gallon for a solvent of medium-range Btu content, depending mainly on the Btu content. The purer solvents can potentially be recovered and sold, reducing the disposal charge, or used as a fuel for the incineration of wastes with a higher water content. Those lower Btu content wastes may vary from $0.35 to $0.60 per gallon for those with high water content; perhaps up to $1.00 for those with high chlorine content as well.

Since the actual quantities of medicinals which are produced in an operation are often difficult to determine, we based the plant size on the number of production workers. A typical operation producing organic medicinal chemicals has 300 production workers. In other industries, the production is related to the number of production workers. That ratio remains relatively constant from plant to plant within an industry. Within the pharmaceutical industry, where the number of intermediate production steps can range from 1 to



[†] Source: Arthur D. Little, Inc., estimates

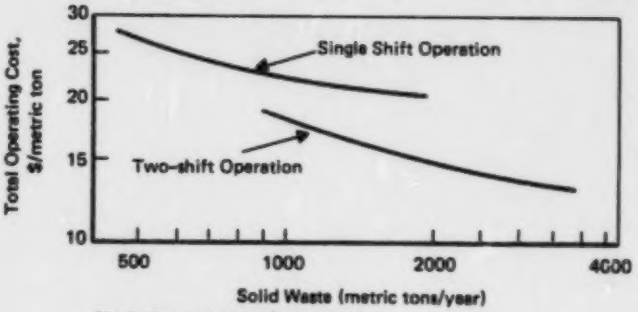
FIGURE 5.3-A IN-PLANT STORAGE AND LANDFILL CHARGES[†]



*ENR Construction Cost Index: 1158

[†] Source: Arthur D. Little, Inc., estimates.

FIGURE 5.3-B GENERAL INDUSTRIAL SOLID WASTE INCINERATION – CAPACITY RANGES AND INVESTMENT COSTS*[†]



*Includes capital-related charges.

[†] Source: Arthur D. Little, Inc., estimates.

FIGURE 5.3-C GENERAL INDUSTRIAL SOLID WASTE INCINERATION OPERATING COSTS*[†]

## TABLE 5.3-C

## CAPITAL INVESTMENT FOR INDUSTRIAL SOLID WASTE INCINERATION[†]

| Capacity | 600 lb/hr | 1200 lb/hr | 2500 lb/hr |
|---|---|---|---|
| Annual Capacity (single-shift operation) | 450 tons[*] | 900 tons[**] | 1875 tons[***] |
| Type | Batch | Batch | Semi-Automatic |
| Capital Cost | | | |
| Incinerator | $25,000 | $45,000 | $100,000 |
| Freight | 2,000 | 3,000 | 5,000 |
| Installation[+] (includes foundations, electrical, plumbing, oil storage) | 5,000 | 8,000 | 15,000 |
| Total Fixed Capital Investment (FCI) | 32,000 | 56,000 | 120,000 |
| Engineering @ 10% of FCI | 3,000 | 5,000 | 12,000 |
| Contractor's Fee @ 7% of FCI | 2,000 | 3,000 | 8,000 |
| Contingency @ 15% FCI | 5,000 | 8,000 | 18,000 |
| Total | $42,000 | $72,000 | $158,000 |

[*] 410 metric tons

[**] 820 metric tons

[***] 1700 metric tons

[+] Installation costs for an incinerator within an operating plant are lower than those for for an incinerator located in areas where these facilities are not already available.

[†] Source: Arthur D. Little, Inc., estimates.

15, we studied the various plants for which production figures were available and found that for operations of approximately the same complexity the production per production worker stays relatively constant also. Ratios varied from 8000 pounds per year per production worker* to 30,000 to 40,000 pounds per year per production worker for large-scale operations making relatively simple products such as aspirin.

The costs of treatment and disposal of hazardous wastes from organic medicinal chemical active ingredient production for a typical plant of 300 production workers are presented in Tables 5.4.2.1-A,-B,-C, and -D. There are smaller operations in the industry ranging down to almost 100 production workers. Few facilities can operate with fewer than this number. Some of the larger operations employ close to 1000 production workers. The problems and the associated costs per amount of waste are generally of the same magnitude as the typical plant.

### *5.4.2.2 Inorganic Medicinal Chemicals*

No individual costs have been developed for the treatment and disposal of inorganic medicinal chemical wastes. We found only one hazardous waste in our survey. We have included its treatment and disposal cost in the overall number for the organic medicinal chemical hazardous waste treatment and disposal cost. We have estimated that the treatment and disposal cost for this waste is approximately $50 per metric ton.

### *5.4.2.3 Fermentation Products*

As we have indicated in Tables 5.4.2.3-A and -B, although the plant size varies, both the large and small plants incur the same average treatment and disposal cost of 14¢/kg of product and $120/metric ton of waste to dispose of a material which is a waste solvent concentrate containing about 50% solids.

### *5.4.2.4 Botanicals*

We have identified three hazardous wastes from the production of botanicals, specifically alkaloids. These materials are an aqueous solvent with 50% solids, a halogenated waste solvent, and a non-halogenated waste solvent. Each of these waste streams was disposed of by incineration. Although there are onsite facilities for incineration of these wastes, as our example we have chosen a typical plant which is using incineration by contractor offsite. The average treatment and disposal costs of these wastes range from $68/metric ton of waste for the non-halogenated waste solvent to $144/metric ton of waste for the aqueous solvent to a high of $180/metric ton of waste for the halogenated waste solvent. Tables 5.4.2.4-A, -B, and -C describe the costs associated with a typical botanical production operation.

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* For operations making widely diverse products in batch operations where many products were made only once per year with the production lasting anywhere from one day to three months.

### *5.4.2.5 Drugs from Animal Sources*

For our typical plant we have chosen a plant with 20 employees manufacturing insulin. The hazardous waste stream from this production facility is an aqueous alcohol with organic solids. It is typically 25% alcohol, 25% solids, and 50% water. This waste is disposed of by incineration by a contractor offsite. The costs average $50/kg of product or $142/metric ton of waste. Table 5.4.2.5 describes the costs associated with a typical operation in which drugs are produced from animal sources.

### *5.4.2.6 Biologicals*

Producing plasma protein fractions represents a typical production scenario for a biological products plant. We have based our estimates of disposal costs on such a plant. The representative production capacity for this plant is a 500-liter batch of input plasma. The associated hazardous waste load from this batch is about 2500 liters of aqueous alcohol. This corresponds to a hazardous waste load per unit of production of 5 liters of waste per liter of plasma. This results in an average treatment and disposal cost of 40¢/liter of input plasma. Table 5.4.2.6 describes the costs associated with a typical biological operation.

## 5.4.3 Formulation and Packaging (SIC 2834)

Finished pharmaceutical preparations are made in the formulation and packaging operation. The hazardous waste stream from this operation consists of a portion of the returned goods and reject materials. A typical plant would have 200 production employees and would operate 250 days per year. Because of the variety of products, it is difficult to assign a representative plant capacity to these operations. We have therefore described the plant capacity both in terms of the value of shipments and the value added in that processing operation. The representative plant we have chosen has $11,000,000 value added and a $14,000,000 value of the shipments. The average product value added annually per employee is $55,000; the average value of shipment annually per employee is $70,000. The hazardous waste load from this facility annually is about 18 metric tons of returned goods and reject material. Under Level I technology, which is described as crushing this material onsite and having a contractor handle the landfill and the sanitary landfill offsite, the cost amounts to about $28 per metric ton of waste. Incineration of this waste by a contractor offsite raises the average treatment and disposal cost to $67 per metric ton of waste.

Table 5.4.3 describes the waste volume and treatment costs of a typical formulation and packaging operation.

## TABLE 5.4.2.1-A

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; ORGANIC MEDICINAL CHEMICALS WASTE STREAM – NON-HALOGENATED WASTE SOLVENT[†]

Plant description: plant with 300 employees

| | |
|---|---|
| Representative production schedule, days/year: | 250 |
| Representative plant capacity: million kg/year: | 1.0 |
| Average product value per unit of production, $/kg | 22 |
| Process hazardous waste load in million kg/year: | |
| Waste solvent, non-halogenated; | 0.7 |
| Waste solvent, halogenated; | 0.1 |
| Potentially hazardous high inert content wastes; | 0.05 |
| Heavy metal waste | – |
| Organic chemical residues | 0.4 |
| Hazardous waste load (Non-halogenated waste solvent) million/kg year: | 0.7 |
| Hazardous waste load per unit of production: kg/kg | 0.7 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 1,000 | as Level I | as Level I |
| Contract disposal charges | 46,400 | ↓ | ↓ |
| Total Annual Costs | 47,400 | ↓ | ↓ |
| Average Treatment/Disposal Cost | | ↓ | ↓ |
| per Unit of Production, $/kg | $0.047 | ↓ | ↓ |
| per metric ton of waste | $68 | ↓ | ↓ |

Level I – Incineration by contractor off-site
Level II – as Level I
Level III – as Level I

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.1-B

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; ORGANIC MEDICINAL CHEMICALS WASTE STREAM – HALOGENATED WASTE SOLVENT[†]

| | |
|---|---|
| Plant description: plant with 300 employees | |
| Representative production schedule, days per year | 250 |
| Representative plant capacity: million kg/year: | 1.0 |
| Average product value per unit of production, $/kg | 22 |
| Process hazardous waste load in million kg/year: | |
| Waste solvent, non-halogenated; | 0.7 |
| Waste solvent, halogenated; | 0.1 |
| Potentially hazardous high inert content wastes; | 0.05 |
| Heavy metal waste | – |
| Organic chemical residues | 0.4 |
| Hazardous waste load (halogenated waste solvent) million kg/year: | 0.1 |
| Hazardous waste load per unit of production: kg/kg | 0.1 |

| | Level of Treatment | | |
|---|---|---|---|
| Cost – ($) | Level I | Level II | Level III |
| Transportation | 160 | as Level I | as Level I |
| Contract disposal charges | 18,280 | | |
| Total Annual Costs | 18,440 | | |
| Average treatment/disposal cost per unit of production, | $0.018/kg | | |
| per metric ton of waste | $184 | | |

Level I – Incineration by contractor off-site
Level II – as Level I; with energy and resource recovery at contractor's site
Level III – as Level II

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.1-C

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; ORGANIC MEDICINAL CHEMICALS WASTE STREAM: POTENTIALLY HAZARDOUS HIGH INERT CONTENT WASTES[†]

| | |
|---|---|
| Plant description: plant with 300 employees | |
| Representative production schedule, days per year | 250 |
| Representative plant capacity: million kg/year: | 1.0 |
| Average product value per unit of production, $/kg | 22 |
| Process hazardous waste load: million kg/year: | |
| Waste solvent, non-halogenated; | 0.7 |
| Waste solvent, halogenated; | 0.1 |
| Potentially hazardous high inert content wastes; | 0.05 |
| Heavy metal waste | – |
| Organic chemical residues | 0.4 |
| Hazardous waste load (potentially hazardous high inert content wastes), million kg/year: | 0.05 |
| Hazardous waste load per unit of production: kg/kg | 0.05 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation Cost | 163 | 163 | as Level II |
| Contractor Incineration Charge | 730 | 730 | |
| Contractor Landfill Charge | 198 | 198 | |
| Neutralization Cost | – | 730 | |
| Contractor Secured Landfill Charge | 438 | 438 | |
| Total Annual Costs | 1,529 | 2,259 | |
| Average treatment/disposal cost | | | |
| per unit of production | $1.53/1000 kg | $2.26/1000 kg | |
| per metric ton of waste | $26 | $43 | |

Level I – Incineration by contractor off-site for solvent containing waste; disposal by contractor in secure chemical landfill for waste containing corrosives or trace amounts of heavy metal.*

Level II – Incineration by contractor off-site for solvent containing waste; treatment (neutralization) by contractor prior to disposal by contractor in secure chemical landfill for waste containing corrosives or trace amounts of heavy metal.

Level III – as Level II

*If this plant were to landfill the solvent containing waste (as described in Table 4.5.3-A) and landfill the waste containing corrosives or trace amounts of heavy metal, then the associated costs for treatment and disposal would be $0.77 per 1000 kg product ($13 per metric ton of waste).

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.1-D

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; ORGANIC MEDICINAL CHEMICALS WASTE STREAM – ORGANIC CHEMICAL RESIDUES[†]

| | |
|---|---|
| Plant description: plant with 300 employees | |
| Representative production schedule, days/year: | 250 |
| Representative plant capacity: million kg/year: | 1.0 |
| Average product value per unit of production: $/kg | 22 |
| Process hazardous waste load in million kg/year: | |
| Waste solvent, non-halogenated; | 0.7 |
| Waste solvent, halogenated; | 0.1 |
| Potentially hazardous high inert content wastes; | 0.05 |
| Heavy metal waste | – |
| Organic chemical residues | 0.4 |
| Hazardous waste load (organic chemical residues) million kg/year: | 0.4 |
| Hazardous waste load per unit of production: kg/kg | 0.4 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 600 | as Level I | as Level I |
| Contract disposal charges | 39,400 | ↓ | ↓ |
| Total Annual Costs | 40,000 | ↓ | ↓ |
| Average treatment/disposal cost | | ↓ | ↓ |
| per unit of production | $0.04/kg | ↓ | ↓ |
| per metric ton of waste | $100 | ↓ | ↓ |

Level I – Incineration by contractor off-site*

Level II – as Level I

Level III – as Level I

---

*If this plant were to landfill these wastes as described in Table 4.5.2, the associated costs for treatment and disposal would be $0.0034 per kg product ($8.50 per metric ton of waste). Larger facilities, such as the one described on this page, do not landfill these residues.

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.3-A

## ACTIVE INGREDIENT PRODUCTION; FERMENTATION PRODUCTS; PENICILLIN WASTE STREAM – WASTE SOLVENT CONCENTRATE (50% SOLIDS)[†]

Plant description: small plant (with solvent extraction)

| | |
|---|---|
| Representative production schedule, days per year: | 350 |
| Representative plant: 200,000-gallon fermentor capacity. Product, million kg/year: | 0.95 |
| Average product value per unit of production, $/kg | 22 |
| Hazardous waste load (waste solvent concentrate, 50% solids), million kg/year: | 1.14 |
| Hazardous waste load per unit of production: kg/kg | 1.20 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 1,730 | as Level I | as Level I |
| Contract disposal charges | 133,000 | | |
| Total Annual Costs | 134,730 | | |
| Average treatment/disposal cost | | | |
| per unit of production | $0.14/kg | | |
| per metric ton of waste | $120 | | |

Level I – Incineration by contractor off-site

Level II – as Level I

Level III – as Level I

[†] **Source:** Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.3-B

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; FERMENTATION PRODUCTS; PENICILLIN WASTE STREAM — WASTE SOLVENT CONCENTRATE (50% SOLIDS)[†]

| | |
|---|---|
| Plant description: large plant (with solvent extraction) | |
| Representative production schedule, days per year: | 350 |
| Representative plant: 600,000-gallon fermentor capacity<br>Product, million kg/year: | 2.9 |
| Average product value per unit of production, $/kg | 22 |
| Hazardous waste load (waste solvent concentrate, 50% solids), million kg/year: | 3.48 |
| Hazardous waste load per unit of production: kg/kg | 1.20 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost — ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 5,280 | as Level I | as Level I |
| Contract disposal charges | 406,000 | | |
| Total Annual Costs | 411,280 | | |
| Average treatment/disposal cost | | | |
| per unit of production | $0.14/kg | | |
| per metric ton of waste | $120 | | |

Level I — Incineration by contractor off-site

Level II — as Level I

Level III — as Level I

---

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.4-A

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; BOTANICALS; ALKALOIDS WASTE STREAM – AQUEOUS SOLVENT WITH SOLIDS (30% SOLVENT, 20% WATER, 50% SOLIDS)[†]

| | |
|---|---|
| Plant description: typical size industrial plant with 20 employees | |
| Representative production schedule, days per year: | 250 |
| Representative plant capacity, kg/year: | 680 |
| Average product value per unit of production, $/kg | 11,000 |
| Process hazardous waste load in thousand $m^3$/year: | |
| Aqueous solvent with 50% solids | 0.09 |
| Halogenated waste solvent | 0.005 |
| Non-halogenated waste solvent | 0.020 |
| Hazardous waste load (aqueous solvent with solids 30% solvent, 20% water, 50% solids) thousand $m^3$/year: | 0.09 |
| Hazardous waste load per unit of production: $m^3$/kg | 0.13 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 160 | as Level I | as Level I |
| Contract disposal charges | 12,500 | ↓ | ↓ |
| Total Annual Costs | 12,760 | | |
| Average treatment/disposal cost | | | |
| per unit of production | $18.8/kg | | |
| per metric ton of waste | $144 | | |

Level I – Incineration by contractor off-site

Level II – as Level I

Level III – as Level I

---

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.4-B

## TREATMENT AND DISPOSAL COSTS
## ACTIVE INGREDIENT PRODUCTION; BOTANICALS; ALKALOIDS
## WASTE STREAM – HALOGENATED WASTE SOLVENT[†]

Plant description: typical size industrial plant with 20 employees

| | |
|---|---|
| Representative production schedule, days per year: | 250 |
| Representative plant capacity: kg/year: | 680 |
| Average product value per unit of production, $/kg | 11,000 |
| Process hazardous waste load in thousand $m^3$/year: | |
| Aqueous solvent with 50% solids | 0.09 |
| Halogenated waste solvent | 0.005 |
| Non-halogenated waste solvent | 0.020 |
| Hazardous waste load (halogenated waste solvent, thousand $m^3$/year): | 0.005 |
| Hazardous waste load per unit of production: $m^3$/kg | 0.007 |

| Cost – ($) | Level I | Level II | Level III |
|---|---|---|---|
| | | as Level I | as Level I |
| Transportation | 20 | ↓ | ↓ |
| Contract disposal charges | 1,000 | ↓ | ↓ |
| Total Annual Costs | 1,020 | ↓ | ↓ |
| Average treatment/disposal cost | | | |
| per unit of production | $1.5/kg | ↓ | ↓ |
| per metric ton of waste | $180 | ↓ | ↓ |

Levels of Treatment (spanning Level I – Level III)

Level I – Incineration by contractor off-site

Level II – as Level I

Level III – as Level I

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.4-C

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; BOTANICALS; ALKALOIDS WASTE STREAM – NON-HALOGENATED WASTE SOLVENT[†]

Plant description: typical size industrial plant with 20 employees

| | |
|---|---|
| Representative production schedule, days per year: | 250 |
| Representative plant capacity, kg/year: | 680 |
| Average product value per unit of production, $/kg | 11,000 |
| Process hazardous waste load in thousand $m^3$/year: | |
| Aqueous solvent with 50% solids | 0.09 |
| Halogenated waste solvent | 0.005 |
| Non-halogenated waste solvent | 0.020 |
| Hazardous waste load (non-halogenated waste solvent, thousand $m^3$/year): | 0.020 |
| Hazardous waste load per unit of production: $m^3$/kg | 0.03 |

| | Levels of Treatment | | |
|---|---|---|---|
| Cost – ($) | Level I | Level II | Level III |
| Transportation | 80 | as Level I | as Level I |
| Contract disposal charges | 1,040 | ↓ | ↓ |
| Total Annual Costs | 1,120 | ↓ | ↓ |
| Average treatment/disposal cost | | ↓ | ↓ |
| per unit of production | $1.60/kg | ↓ | ↓ |
| per metric ton of waste | $68 | ↓ | ↓ |

Level I – Incineration by contractor offsite

Level II – as Level I

Level III – as Level I

[†] Source: Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.5

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; DRUGS FROM ANIMAL SOURCES; INSULIN WASTE STREAM – AQUEOUS ALCOHOL WITH ORGANIC SOLIDS (25% ALCOHOL, 25% SOLIDS, 50% WATER)[†]

| | |
|---|---|
| Plant description: typical size industrial plant with 20 employees | |
| Representative production schedule, days per year: | 250 |
| Representative plant capacity, kg/year: | 284 |
| Average product value per unit of production, $/kg | 11,000 |
| Hazardous waste load (aqueous alcohol with organic solids, 25% alcohol, 25% solids, 50% water), thousand $m^3$/year: | 0.10 |
| Hazardous waste load per unit of production: $m^3$/kg | 0.35 |

| | **Levels of Treatment** | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Transportation | 400 | as Level I | as Level I |
| Contract disposal charges | 13,900 | | |
| Total Annual Costs | 14,300 | | |
| Average treatment/disposal cost | | | |
| per unit of production | $50/kg | | |
| per metric ton of waste | $142 | | |

Level I – Incineration by contractor off-site

Level II – as Level I

Level III – as Level I

---

[†] **Source:** Arthur D. Little, Inc., estimates.

## TABLE 5.4.2.6

## TREATMENT AND DISPOSAL COSTS: ACTIVE INGREDIENT PRODUCTION; BIOLOGICAL PRODUCTS; PLASMA PROTEIN FRACTIONS WASTE STREAM – AQUEOUS SOLVENT[†]

| | |
|---|---|
| Plant description: typical size industrial plant | |
| Representative production schedule, days/year | 250 |
| Representative production capacity: 500-liter batch of input plasma | |
| Average product value per unit of production, $/kg | N.A.* |
| Hazardous waste load (aqueous alcohol, liters/batch) | 2,500 |
| Hazardous waste load per unit of production: liters/liter of plasma | 5 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Contract disposal charges per batch | 200 | as Level I | as Level I |
| Average treatment/disposal cost per liter of plasma | $0.40/liter of input plasma | ↓ | ↓ |

Level I – Incineration by contractor off-site

Level II – as Level I

Level III – as Level I

*N.A. = not available

[†] **Source:** Arthur D. Little, Inc., estimates.

# TABLE 5.4.3

## TREATMENT AND DISPOSAL COSTS: FORMULATION AND PACKAGING (FINISHED PHARMACEUTICAL PREPARATIONS) WASTE STREAM – RETURNED GOODS AND REJECT MATERIAL[†]

| | |
|---|---|
| Plant description: plant with 200 employees | |
| Representative production schedule, days/year: | 250 |
| Representative plant capacity: $11 million value added<br>$14 million value of shipments | |
| Average product value added per employee, $/year | $55,000 |
| Average value of shipments per employee, $/year | $70,000 |
| Hazardous waste load, returned goods and reject material, | |
| metric tons/year | 18 |
| kg/year/employee | 90 |

| | Levels of Treatment | | |
|---|---|---|---|
| **Cost – ($)** | **Level I** | **Level II** | **Level III** |
| Crushing | 100 | – | as Level II |
| Transportation | 200 | 200 | |
| Landfill Charge | 200 | – | |
| Incineration Charge | – | 1,000 | |
| Total Annual Costs | 500 | 1,200 | |
| Average treatment/disposal cost | | | |
| per metric ton of waste | $27.80 | $66.70 | |
| per pound of waste | $0.013 | $0.03 | |

Level I – crush on-site and landfill in sanitary landfill off-site by contractor

Level II – Incineration by contractor off-site

Level III – as Level II

[†] **Source:** Arthur D. Little, Inc., estimates.

# APPENDIX A*

## DESCRIPTION OF HAZARD GRADES

### HAZARD CATEGORY I – FIRE

| | |
|---|---|
| Grade 0 | **Insignificant Hazard:** Includes chemicals that are essentially noncombustible. |
| Grade 1 | **Slightly Hazardous:** Includes chemicals having a closed-cup flash point above 140°F (60°C). |
| Grade 2 | **Hazardous:** Includes combustible chemicals having a closed-cup flash point below 140°F (60°C) and above 100°F (37.8°C). |
| Grade 3 | **Highly Hazardous:** Includes flammable liquids having a closed-cup flash point below 100°F (37.8°C) and a boiling point under standard conditions above 100°F (37.8°C). |
| Grade 4 | **Extremely Hazardous:** Includes volatile liquids or liquefied gaseous materials having a flash point below 100°F (37.8°C) and a boiling point below 100°F (37.8°C). |

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*National Academy of Sciences Hazard Classification Scheme.

## HAZARD CATEGORY II – LIQUID CONTACT WITH SKIN AND EYES

| | |
|---|---|
| Grade 0 | Insignificant Hazard: Liquids in this category are all those not described below. |
| Grade 1 | Slightly Hazardous: Liquids that are corrosive to the eyes according to the definition in 16 CFR 1500.3(c) (3) and the test procedure in 16 CFR 1500.42 |
| Grade 2 | Moderately Hazardous: Liquids in this category are:<br>a. Liquids that are corrosive according to the test procedure described in 46 CFR 146.23-1.<br>b. Materials that are transported as liquids at 140°F (60°) or above.<br>c. Liquefied gases that are capable of causing freeze burns. |
| Grade 3 | Highly Hazardous: Liquids in this category have an $LD_{50}$* of more than 20 mg/kg of body weight when administered by continuous contact for 24 hours or less with the bare skin of rabbits, according to the test procedure described in 21 CFR Section 191.10 of the Code of Federal Regulations. |
| Grade 4 | Extremely Hazardous: Liquids in this category have an $LD_{50}$* of 20 mg/kg or less or body weight when administered by continuous contact for 24 hours or less with the bare skin of rabbits, according to the test procedure described in 21 CFR Section 191.10 of the Code of Federal Regulations. |

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*$LD_{50}$: that dose likely to kill one-half of a group of animals within 14 days.

## HAZARD CATEGORY III – INHALATION OF VAPORS
### (Occasional Short-Term)

| | |
|---|---|
| Grade 0 | Insignificant Hazard: Liquids in this category are all those not described below. |
| Grade 1 | Slightly Hazardous: Liquids in this category cause dizziness and unsteadiness in 30 minutes or less upon exposure to an atmosphere saturated with vapor at 122°F (50°C).* |
| Grade 2 | Moderately Hazardous: Liquids in this category have an $LC_{50}$** in air of more than 200 ppm, but not more than 2000 ppm by volume of vapor; or more than 2 mg/l, but not more than 20 mg/l of mist when administered by continuous inhalation for one hour or less to both male and female albino rats (young adults), provided the Coast Guard finds that such concentration is likely to be encountered by man under any reasonably foreseeable condition of transportation.*<br>Liquids in this category may produce sufficient irritation of the eyes or respiratory tract to cause temporary incapacitation. This includes lachrymators and those corrosive liquids as defined above in Hazard Category I that have a vapor pressure at 122°F (50°C) or 10 mm Hg or more.* |
| Grade 3 | Highly Hazardous: Liquids in this category have an $LC_{50}$** in air of more than 50 ppm but not more than 200 ppm by volume of vapor, or more than 0.50 mg/l, but not more than 2 mg/l, of mist when administered by continuous inhalation for one hour or less to both male and female albino rats (young adults), provided the Coast Guard finds that such concentration is likely to be encountered by man under any reasonably foreseeable condition of transportation.* |
| Grade 4 | Extremely Hazardous: Liquids in this category have an $LC_{50}$** in air of 50 ppm by volume or less of vapor, or 0.5 mg/l or less of mist when administered by continuous inhalation for one hour or less to both male and female albino rats (young adults), provided the Coast Guard finds that such concentration is likely to be encountered by man under any reasonably foreseeable condition of transportation. |

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*During transportation emergencies involving liquids (ruptures, spills, etc.) the degree of personnel hazard is increased by rapid evaporation. If the ratio of the evaporation rate for the test material to that of n-butyl acetate at 122°F (50°C) under the same test conditions is 0.8 or less, the test material should be given the next higher rating with a notation to this effect. An appropriate test procedure has been described.

**$LC_{50}$: that concentration which, over a given period of time, is likely to kill one-half the test animal species.

## HAZARD CATEGORY IV – GAS INHALATION

| | |
|---|---|
| Grade 0 | Grade 0 is not applicable since no gas has an insignificant hazard. |
| Grade 1 | Slightly Hazardous: Gases in this category are all those *not* described below, since the release of a gas into a confined space may displace sufficient oxygen to create a significant hazard to life. |
| Grade 2 | Moderately Hazardous: Gases in this category have an $LC_{50}$* in air of more than 200 ppm, but not more than 2000 ppm, by volume of gas when administered by continuous inhalation for one hour or less to both male and female albino rats (young adults). Gases in this category may product sufficient irritation of the eyes or respiratory tract to cause temporary incapacitation. This includes lachrymators. |
| Grade 3 | Highly Hazardous: Gases in this category have an $LC_{50}$* of more than 50 ppm, but not more than 200 ppm as described in Grade 3 of Hazard Category III. |
| Grade 4 | Extremely Hazardous: Gases in this category have an $LC_{50}$* of 50 ppm or less as described in Grade 4 of Hazard Category III. |

## HAZARD CATEGORY V** – HAZARD RATING FOR PREPARED INHALATION OF GASES AND VAPORS

| | |
|---|---|
| Grade 0 | Insignificant Hazard: Materials in this category are all those *not* described below and having standards established by the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA), as in 29 CFR Subpart G, Section 1910.93, of 1000 ppm or more. |
| Grade 1 | Slightly Hazardous: Materials in this category have standards established by OSHA of 100 ppm or more, but less than 1000 ppm. |
| Grade 2 | Moderately Hazardous: Materials in this category have standards established by OSHA of 10 ppm or more, but less than 100 ppm. |
| Grade 3 | Highly Hazardous: Materials in this category have standards established by OSHA of 1 ppm or more, but less than 10 ppm. |
| Grade 4 | Extremely Hazardous: Materials in this category have Occupational Safety and Health Standards established by OSHA of less than 1 ppm. |

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*$LC_{50}$: that concentration which, over a given period of time, is likely to kill one-half the test animal species.

**OSHA standards are applicable to a normal working situation, i.e., 8 hours per day, 5 days per week.

## HAZARD CATEGORY VI – WATER POLLUTION RATING – HUMAN TOXICITY

| Grade | Description | $LD_{50}$ |
|---|---|---|
| 0 | Insignificant Hazard | Above 5000 mg/kg |
| 1 | Slightly Hazardous | 500-5000 mg/kg |
| 2 | Moderately Hazardous | 50-500 mg/kg |
| 3 | Highly Hazardous | 5-50 mg/kg |
| 4 | Extremely Hazardous | Below 5 mg/kg |

## HAZARD CATEGORY VII – AQUATIC TOXICITY RATING

| Grade | Description | $TL_m$ Concentration |
|---|---|---|
| 0 | Insignificant Hazard | >1000 mg/l |
| 1 | Practically Nontoxic | 100-1000 mg/l |
| 2 | Slightly Toxic | 10-100 mg/l |
| 3 | Moderately Toxic | 1-10 mg/l |
| 4 | Highly Toxic | <1 mg/l |

## HAZARD CATEGORY VIII – WATER REACTION RATING

| | |
|---|---|
| Grade 0 | Insignificant Hazard: No known hazardous reaction with water. |
| Grade 1 | Slightly Hazardous: Chemical or physical reaction with water may occur. Unlikely to be hazardous under conditions of water transportation. Examples are chlorine, bromine, ethylene oxide, propylene oxide, propionic anhydride, stabilized benzoyl chloride, and acetic anhydride. |
| Grade 2 | Hazardous Reaction: Examples are anhydrous ammonia, hydrogen fluoride, and hydrogen chloride. |
| Grade 3 | Highly Hazardous (Vigorous Reaction): Examples are oleum, 72%-98% sulfuric acid, ethyl trichlorosilane, and chloroacetyl chloride. |
| Grade 4 | Extremely Hazardous (Violent Reaction): Likely if mixed with water. Examples are sulfur trioxide, chlorosulfonic acid, aluminum triethyl, unstabilized benzoyl chloride, methyl trichlorosilane, and acetyl chloride. |

## HAZARD CATEGORY IX – SELF-REACTION RATING

| | |
|---|---|
| Grade 0 | Insignificant Hazard: No appreciable self-reaction. |
| Grade 1 | Slightly Hazardous: Chemicals known to undergo polymerization or other self-reaction under certain conditions. Due to low reactivity or low heat evolution, they are unlikely to lead to a hazardous situation in bulk water transportation. |
| Grade 2 | Hazardous: Chemicals that may undergo polymerization or other self-reaction if contaminated by an initiator for such process. The results may be hazardous. They are not considered to require a stabilizer or inhibitor for safe shipment under normal conditions. |
| Grade 3 | Highly Hazardous: Chemicals that may underto a hazardous self-reaction and are considered to require special handling, such as incorporation of a stabilizer or polymerization inhibitor to ensure safety in bulk water transportation. |
| Grade 4 | Extremely Hazardous: Chemicals that can undergo self-oxidation, and/or polymerization, possibly causing explosions or detonations. |

# APPENDIX B

## PROPERTIES OF HAZARDOUS CONSTITUENTS

### EXPLANATION OF SPECIAL TERMS

Several of the terms used in the following tables may not be clear to the average reader. Therefore, we have prepared short explanations that will be useful in interpreting the data.

- **Physical Form** – The statement indicates whether the chemical is a solid, liquid, or gas after it has reached equilibrium with its surroundings at "ordinary" conditions of temperature and pressure (15°C and 1 atmosphere).

- **Specific Gravity** – The specific gravity of a chemical is the ratio of the weight of the solid or liquid to the weight of an equal volume of water at 4°C (or at some other specified temperature).

- **Flash Point** – The flash point is defined as the lowest temperature at which vapors above a volatile combustible substance will ignite in air when exposed to a flame. Depending on the test method used, the values given are either Tag closed cup (C.C.) (ASTM D56) or Cleveland open cup (O.C.) (ASTM D93). The values give an indication of the relative flammability of the chemical. In general, the open-cup value is about 10° to 15°F higher than the closed-cup value.

- **Boiling Point at 1 Atmosphere** – This value is the temperature of a liquid when its vapor pressure is 1 atmosphere. For example, when water is heated to 100°C (212°F), its vapor pressure rises to 1 atmosphere and the liquid boils.

- **Melting Point** – The melting point is the temperature at which a solid changes to a liquid.

- **Chemical Composition** – This has been limited to a commonly used one-line formula.

- **Molecular Weight** – The value given is the weight of a molecule of the chemical relative to a value of 12 for one atom of carbon.

- **Heat of Combustion** – The value is the amount of heat liberated when the specified weight is burned in oxygen at 25°C. The products of combustion, including water, are assumed to remain as gases; the value given is usually referred to as the "lower heat value." The negative sign before the value indicates that heat is given off when the chemical burns. Units are calories per gram.

- **Solubility** – The value represents the grams of a chemical that will dissolve in 100 grams of pure water. Solubility usually increases when the temperature increases. The following terms are used when numerical data are either unavailable or not applicable:

  "Miscible" means that the chemical mixes with water in all proportions. "Insoluble" usually means that 1 gram of the chemical does not dissolve entirely in 100 grams of water.

- **$TL_m$ (Aquatic Toxicity)** – $TL_m$ (Median Tolerance Limit) means that approximately 50% of the fish will die under the conditions of concentration and time given. The form of data presentation used by the Environmental Protection Agency's "Oil and Hazardous Material-Technical Assistance Data System (OHM-TADS)" is used here. Reading from left to right and separated by slashes (/) are the following data:

  Concentration in parts per million by weight (or milligrams per liter) at which the chemical was tested;

  Time of exposure in hours;

  Name of the aquatic species studied (only data on fish are given here);

- **TLV (Threshold Limit Value)** – The threshold limit value is usually expressed in units of parts per million (ppm) – i.e., the parts of vapor (gas) per million parts of contaminated air by volume at 25°C (77°F) and atmospheric pressure. For a chemical that forms a fine mist or dust, the concentration is given in milligrams per cubic meter ($mg/m^3$). The TLV is defined as the concentration of the substance in air that can be breathed for five consecutive eight-hour workdays (40-hour work week) by most people without adverse effect.* As some people become ill after exposure to concentrations lower than the TLV, this value cannot be used to define exactly what is a "safe" or "dangerous" concentration.

- **$LD_{50}$ (Oral Toxicity)** – The term $LD_{50}$ signifies that about 50% of the animals given the specified dose by mouth will die. All $LD_{50}$ values listed are for rats.

---

*American Conference of Governmental Industrial Hygienists, "Threshold Limit Values for Substance in Workroom Air, Adopted by ACGIH for 1972."

## TABLE B-1

## PROPERTIES OF ACETONE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.791
Flash Point: 4°F O.C., 0°F C.C.
Boiling point at 1 atm: 56.1°C
Melting point: -94.7°C
% Cl:

Chemical composition: $CH_3COCH_3$
Molecular Weight: 58.08
Heat of Combustion: -6808 cal/g
Solubility: Complete
Odor: Sweetish

**Biological Properties**

Toxicity:
$TL_m$: 13,000 ppm/48 hr/mosquito fish
TLV: 1000 ppm
$LD_{50}$: $>$5000 mg/kg

## TABLE B-2

## PROPERTIES OF ACETONITRILE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.787
Flash Point: 42°F O.C.
Boiling point at 1 atm: 81.6°C
Melting point: 45.7°C
% Cl:

Chemical composition: $CH_3CN$
Molecular Weight: 41.05
Heat of Combustion: -7420 cal/g
Solubility: Miscible
Odor: Sweet, ethereal

**Biological Properties**

Toxicity:
$TL_m$: 1150 ppm/24 hr/fathead minnow
TLV: 40 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-3

## PROPERTIES OF AMYL ACETATE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.876
Flash Point: (n-) 91°F, C.C., (iso-) 69°F C.C.
Boiling point at 1 atm: 146°C
Melting point: $<$-100°C
% Cl:

Chemical composition: $CH_3COOC_5H_{11}$
Molecular Weight: 130.19
Heat of Combustion: -7423 cal/g
Solubility: Insoluble
Odor: Banana-like

**Biological Properties**

Toxicity:
$TL_m$:
TLV: 100 ppm
$LD_{50}$: >5000 mg/kg

## TABLE B-4

## PROPERTIES OF BENZENE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.879
Flash Point: 12°F C.C.
Boiling point at 1 atm: 80.1°C
Melting point: 5.5°C
% CL:

Chemical composition: $C_6H_6$
Molecular Weight: 78.11
Heat of Combustion: -9698 cal/g
Solubility: Insoluble
Odor: Aromatic

**Biological Properties**

Toxicity:
$TL_m$: 20 ppm/24 hr/sunfish
TLV: 25 ppm
$LD_{50}$: >5000 mg/kg

## TABLE B-5

## PROPERTIES OF CHLOROFORM

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 1.49
Flash Point: –
Boiling point at 1 atm: 61.2°C
Melting point: -63.5°C
% Cl: 89.09

Chemical composition: $CHCl_3$
Molecular Weight: 119.39
Heat of Combustion: –
Solubility: Insoluble
Odor: Ethereal

**Biological Properties**

Toxicity:
$TL_m$: –
TLV: 25 ppm
$LD_{50}$: >5000 mg/kg

## TABLE B-6

## PROPERTIES OF CHROMIC ANHYDRIDE

**Physical & Chemical Properties**

Physical form: Solid
Specific gravity: 2.70
Flash Point: –
Boiling point at 1 atm:
Melting point: –
% Cl: –

Chemical composition: $CrO_3$
Molecular Weight: 100.01
Heat of Combustion: –
Solubility: Very soluble
Odor: –

Reactivity: Reacts with organic materials rapidly; may cause ignition

**Biological Properties**

Toxicity:
$TL_m$: 52 ppm/96 hr/goldfish
TLV: –
$LD_{50}$: 50-500 mg/kg

## TABLE B-7

## PROPERTIES OF COPPER SULFATE

**Physical & Chemical Properties**

Physical form: Solid

Specific gravity: 2.29

Flash Point: –

Boiling point at 1 atm:

Melting point: –

% Cl:

Chemical composition: $CuSO_4 .5H_2O$

Molecular Weight: 249.7

Heat of Combustion: –

Solubility: Soluble

Odor: –

**Biological Properties**

Toxicity:

$TL_m$: 3.8 ppm/24 hr/rainbow trout

TLV: –

$LD_{50}$: 50-500 mg/kg

## TABLE B-8

## PROPERTIES OF ETHANOL

**Physical & Chemical Properties**

Physical form: Liquid

Specific gravity: 0.790

Flash Point: 55°F C.C., 64°F O.C.

Boiling point at 1 atm: 78.3°C

Melting point: -114°C

% Cl: –

Chemical composition: $C_2H_5OH$

Molecular Weight: 46.07

Heat of Combustion: -6425 cal/g

Solubility: Miscible

Odor: Like whiskey

**Biological Properties**

Toxicity:

$TL_m$: 250 ppm/6 hr/goldfish

TLV: 1000 ppm

$LD_{50}$: >5000 mg/kg

## TABLE B-9

## PROPERTIES OF ETHYLENE DICHLORIDE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 1.253
Flash Point: 60°F O.C., 55°F C.C.
Boiling point at 1 atm: 83.5°C
Melting point: -35.7°C
% Cl: 71.66

Chemical composition: $ClCH_2CH_2Cl$
Molecular Weight: 98.96
Heat of Combustion: 1900 cal/g
Solubility: Insoluble
Odor: Ethereal

**Biological Properties**

Toxicity:
$TL_m$: 150 ppm/ */pin perch
TLV: 50 ppm
$LD_{50}$: 500-5000 mg/kg

*Time of exposure unknown.

## TABLE B-10

## PROPERTIES OF ETHYLENE GLYCOL MONOMETHYL ETHER

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.966
Flash Point: 120°F O.C., 107°F C.C.
Boiling point at 1 atm: 124.5°C
Melting point: -85.1°C
% Cl: –

Chemical composition: $CH_3OCH_2CH_2OH$
Molecular Weight: 76.10
Heat of Combustion: 5,500 cal/g
Solubility: Miscible
Odor: Mild ethereal

**Biological Properties**

Toxicity:
$TL_m$: –
TLV: 25 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-11

## PROPERTIES OF HEPTANE

**Physical & Chemical Properties**

Physical form: Liquid

Specific gravity: 0.6838

Flash Point: 250° F C.C.

Boiling point at 1 atm: 98.4°C

Melting point: -90.6°C

% Cl: –

Chemical composition: $CH_3(CH_2)_5CH_3$

Molecular Weight: 100.21

Heat of Combustion: -10,650 cal/g

Solubility: Insoluble

Odor: Gasoline

**Biological Properties**

Toxicity:

$TL_m$: 4924/24 hr/mosquito fish

TLV: 500 ppm

$LD_{50}$: >15000 mg/kg

## TABLE B-12

## PROPERTIES OF ISOPROPYL ALCOHOL

**Physical & Chemical Properties**

Physical form: Liquid

Specific gravity: 0.785

Flash Point: 65° F O.C., 54° F C.C.

Boiling point at 1 atm: 82.3°C

Melting point: -88.5°C

% Cl: –

Chemical composition: $CH_3CH(OH)CH_3$

Molecular Weight: 60.10

Heat of Combustion: -7,201 cal/g

Solubility: Soluble

Odor: Like ethyl alcohol

**Biological Properties**

$TL_m$: 900-1000 ppm/24 hr/chab

TLV: 400 ppm

$LD_{50}$: >5000 mg/kg

## TABLE B-13

## PROPERTIES OF MERCURY

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 13.56
Flash Point: –
Boiling point at 1 atm: 357°C
Melting point: -38.9°C
% Cl: –

Chemical composition: Hg
Molecular Weight: –
Heat of Combustion: –
Solubility: Insoluble
Odor: –

**Biological Properties**

Toxicity:
$TL_m$: 0.29 ppm/48 hr/marine fish
TLV: 0.05 ng/m$^3$
$LD_{50}$: –

## TABLE B-14

## PROPERTIES OF METHANOL

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.792
Flash Point: 59°F C.C., 61°F O.C.
Boiling point at 1 atm: 64.5°C
Melting point: -97.8°C
% Cl: –

Chemical composition: $CH_3OH$
Molecular Weight: 32.04
Heat of Combustion: -4677 cal/g
Solubility: Miscible
Odor: Faintly sweet

**Biological Properties**

Toxicity:
$TL_m$: 250/4 hr/goldfish
TLV: 200 ppm
$LD_{50}$ >5999 mg/kg

## TABLE B-15

## PROPERTIES OF METHYL ISOBUTYL KETONE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.802
Flash Point: 73°F C.C., 75°F O.C.
Boiling point at 1 atm: 116.2°C
Melting point: -84°C
% Cl: –

Chemical composition: $(CH_3)_2CHCH_2COCH_3$
Molecular Weight: 100.16
Heat of Combustion: -5800 cal/g
Solubility: 2%
Odor: Pleasant ketonic

**Biological Properties**

Toxicity:
$TL_m$: >1000 ppm
TLV: 100 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-16

## PROPERTIES OF METHYLENE CHLORIDE

**Physical & Chemical Properties:**

Physical form: Liquid
Specific gravity: 1.322
Flash Point: –
Boiling point at 1 atm: 39.8°C
Melting point: -96.7°C
% Cl: 83.49

Chemical composition: $CH_2Cl_2$
Molecular Weight: 84.93
Heat of Combustion: –
Solubility: Insoluble
Odor: Aromatic

**Biological Properties**

Toxicity:
$TL_m$: –
TLV: 500 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-17

## PROPERTIES OF NAPHTHA (STODDARD SOLVENT)

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.78
Flash Point: 110°F C.C.
Boiling point at 1 atm: 160-199°C
Melting point: –
% Cl: –

Chemical composition: (mixture)
Molecular Weight: –
Heat of Combustion: -10,100 cal/g
Solubility: Insoluble
Odor: Like kerosene

**Biological Properties**

Toxicity:
$TL_m$: –
TLV: 200 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-18

## PROPERTIES OF n-BUTANOL

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.810
Flash Point: 84°F C.C., 97°F C.C.
Boiling point at 1 atm: 117.7°C
Melting point: -89.3°C
% Cl: –

Chemical composition: $CH_3(CH_2)_2CHOH$
Molecular Weight: 74.12
Heat of Combustion: -7906 cal/g
Solubility: Slightly soluble
Odor: Alcohol-like

**Biological Properties**

Toxicity:
$TL_m$: 1000 ppm/29 hr/goldfish
TLV: 100 ppm
$LD_{50}$: 500-5000 mg/kg

## TABLE B-19

## PROPERTIES OF n-BUTYL ACETATE

**Physical & Chemical Properties**

Physical form: Liquid

Specific gravity: 0.875

Flash Point: 99°F O.C., 75°F C.C.

Boiling point at 1 atm: 126°C

Melting point: -73.5°C

% Cl: –

Chemical composition: $CH_3COO(CH_2)_3CH_3$

Molecular Weight: 116.16

Heat of Combustion: -7294 cal/g

Solubility: Insoluble

Odor: Fruity in low concentrations

**Biological Properties**

Toxicity:

$TL_m$: –

TLV: 150-200 ppm

$LD_{50}$: >5000 mg/kg

## TABLE B-20

## PROPERTIES OF o-XYLENE

**Physical & Chemical Properties**

Physical form: Liquid

Specific gravity: 0.880

Flash Point: 63°F C.C., 75°F O.C.

Boiling point at 1 atm: 144.4°C

Melting point: -25.2°C

% Cl: –

Chemical composition: $o\text{-}C_6H_4(CH_3)_2$

Molecular Weight: 106.16

Heat of Combustion: -9754.7 cal/g

Solubility: Insoluble

Odor: Benzene-like

**Biological Properties**

Toxicity:

$TL_m$: –

TLV: 100 ppm

$LD_{50}$: 50-500 mg/kg

## TABLE B-21

## PROPERTIES OF TOLUENE

**Physical & Chemical Properties**

Physical form: Liquid
Specific gravity: 0.867
Flash Point: 40°F C.C., 55°F O.C.
Boiling point at 1 atm: 110.6°C
Melting point: -95.0°C
% Cl: –

Chemical composition: $C_6H_5CH_3$
Molecular Weight: 92.14
Heat of Combustion: -9686 cal/g
Solubility: Insoluble
Odor: Aromatic

**Biological Properties**

Toxicity:
$TL_m$: 1180 ppm/96 hr/sun fish
TLV: 100 ppm
$LD_{50}$: >5000 mg/kg

## TABLE B-22

## PROPERTIES OF ZINC CHLORIDE

**Physical & Chemical Properties**

Physical form: Solid
Specific gravity: 2.91
Flash Point: –
Boiling point at 1 atm: –
Melting point: 283°C
% Cl: 52.03

Chemical composition: $ZnC1_2$
Molecular Weight: 136.28
Heat of Combustion: –
Solubility: Soluble
Odor: –

**Biological Properties**

Toxicity:
$TL_m$: 7.2 ppm/96 hr/bluegill
TLV: 1 mg/m$^3$ (dust)
$LD_{50}$: 50-500 mg/kg

## GLOSSARY OF TERMS

**Activated Sludge Treatment** – A wastewater treatment process in which biological organisms convert soluble and insoluble pollutants to biological mass (activated sludge) which is then usually removed from the treated wastewater by settling.

**Active Ingredient** – The chemical constituent in a medicinal which is responsible for its activity.

**Analgesics** – Pain-relieving medicinals.

**Ataraxics** – Tranquilizers

**Alkaloids** – Basic (alkaline) nitrogenous botanical products which produce a marked physiological action when administered to animals (or humans).

**Ampoule** – A small, sealed-glass container for one dose of a sterile medicine to be injected hypodermically.

**Antibiotic** – A substance produced by a living organism which has the power to inhibit multiplication of, or to destroy, other organisms, especially bacteria.

**Biological Products** – In the pharmaceutical industry, medicinal products derived from animals or humans, such as vaccines, toxoids, antisera and human blood fractions.

**Blood Fractionation** – The separation of human blood into its various protein fractions.

**BOD – Biochemical Oxygen Demand** – A measure of the amount of oxygen required (and, therefore, the concentration of the pollutants present) in the destruction of pollutant(s) by microorganisms (i.e., activated sludge).

**Botanicals** – Drugs made from a part of a plant, such as roots, bark, or leaves.

**Capsules** – A gelatinous shell used to contain medicinal chemicals; a dosage form for administering medicine.

**Chemical Residues** – Waste materials, such as still bottoms and chemical process "muds" or waste slurries.

**Control Technology** – Method for treatment or disposal for wastes such as neutralization, landfill, and incineration.

**Diatomaceous Earth** – A fine material of uniform particle size used to aid in filtration.

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**Ethical Products** – Pharmaceuticals promoted by advertising to the medical, dental, and veterinary professions.

**Fermentation** – Decomposition or conversion of complex substances to other substances by enzymes produced by microorganisms.

**Fermentor Broth** – A slurry of microorganisms in water containing nutrients (carbohydrates, nitrogen) necessary for the microorganism's growth.

**Filter Cakes** – Wet solids generated by the filtration of solids from a liquid. This filter cake may be a pure material (product) or a waste material containing additional fine solids (i.e., diatomaceous earth) that has been added to aid in the filtration.

**Halogenated Solvent** – An organic liquid chemical containing an attached halogen (chlorine, fluorine, etc.) used for dissolving other substances.

**Hazardous High-Inert Content Wastes** – Those high inert content wastes which contain corrosives, trace amounts of heavy metals, or flammable solvents.

**Hazardous Wastes** – No final judgments are intended by such a classification. Additional information will be required before a definition of hazardous waste can be made.

**Heavy Metals** – Originally defined as a group of metals including lead, zinc, arsenic, mercury, selenium, cadmium, and copper which have an atomic weight greater than iron. In more recent usage, the toxic metals, chromium and vanadium, are also considered to be "heavy (toxic) metals."

**High-Inert Content Wastes** – Waste materials such as filter cakes which contain large amounts of diatomaceous earth, filter aid or activated carbon used to remove color or trace impurities.

**Hormone** – Any of a number of substances formed in the body which activate specifically receptive organs when transported to them by the body fluids.

**IMCO System** – Intergovernmental Maritime Consultative Organization hazardous material determination system.

**Incineration** – Burning under controlled combustion conditions.

**Injectables** – Medicinals prepared in a sterile (buffered) form suitable for administration by injection.

**Iso-Electric Precipitation** – Adjustment of the pH (hydrogen ion concentration) of a solution to cause precipitation of a substance from the solution.

**Land-Destined Process Wastes** – Solids, slurries and liquids currently or previously disposed on land. The term is used to distinguish these wastes from water or air effluents.

**Land Disposal** – Placing waste materials into the land in a specific manner as a method of treatment, storage, or disposal.

**$LD_{50}$** – A dosage level that is lethal to 50% of the test animals to which it is administered.

**Medicinal Chemicals** – Chemicals which have therapeutic value.

**Mycelia** – A mass of filaments which constitutes the vegetative body of fungi. In the industry, the term is commonly used to designate the mixture of cells, filter aid, undigested grain solids, etc., that is filtered off and discarded from all types of fermentations.

**Pharmaceutical** – A medicinal chemical which has been processed into a stable useful dosage form.

**Plasma** – The fluid part of the lymph and of the blood, as distinguished from the corpuscles.

**PMA** – Pharmaceutical Manufacturers Association, which represents 110 pharmaceutical manufacturing firms which, in turn, account for approximately 95 percent of the ethical pharmaceuticals sold in the United States.

**Priority I – Hazardous Waste** – Includes all "elementary" toxic materials, viz., materials which are potentially harmful, regardless of their state of chemical combination. This also includes materials which owe their hazardous properties to their molecular arrangement – and which fall in hazard grades 3 or 4 in Table 3.1.2A.

**Priority II – Hazardous Waste** – These wastes owe their hazardous properties to their molecular arrangement and fall in hazard grades 1 or 2 in Table 3.1.2A.

**Proprietary Products** – Pharmaceuticals promoted by advertising directly to the consumer.

**Sanitary Landfill** – A sanitary landfill is a land disposal site employing an engineered method of disposing of solid wastes on land in a manner that minimizes environmental hazards by spreading the wastes in thin layers, compacting the solid wastes to the smallest practical volume, and applying cover material at the end of each operating day.

**Secure Chemical Landfill** – A landfill that is lined and limited to chemical wastes.

**Serum** – Blood serum containing agents of immunity, taken from an animal made immune to a specific disease by inoculation; it is used as an antitoxin.

**SIC Codes** – Standard Industrial Classification. Numbers used by the U.S. Department of Commerce to denote segments of industry.

**Steroid** – Any one of a large group of multicyclic ring chemical substances related to various alcohols occurring naturally in plants and animals.

**Still Bottom** – The residue remaining after distillation of a material. Varies from a watery slurry to a thick tar which may turn hard when cool.

**Tablet** – A small, disc-like mass of compressed medicinal powder used as a dosage form for administering medicine.

**Technology Level I** – A waste treatment or disposal method that is the broad average of technologies which are currently used in typical facilities.

**Technology Level II** – A waste treatment or disposal method which is the best technology from an environmental and health standpoint that is currently used in at least one pharmaceutical facility.

**Technology Level III** – A waste treatment or disposal method that provides adequate health and environmental protection.

**$TL_m$ – Median Tolerance Limit** – This measure of aquatic toxicity means that approximately 50 percent of the fish will die under the conditions of concentration and time given.

**Toxoid** – Toxin treated to destroy its toxicity, but still capable of inducing antibody formation.

**Vaccine** – A preparation of dead or modified live virus or bacteria introduced into the body to produce immunity to a specific disease by causing the formation of antibodies.

**Virus** – Any of a group of ultramicroscopic or submicroscopic infective agents that cause various diseases; viruses are capable of multiplying in connection with living cells.

**Wastewater** – Process water contaminated to such an extent it is not reusable in the process without repurification.

**Also please note terms appearing in Appendix B.**

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